CB 1/CB 2 receptor ligands and their use in the treatment of pain.

BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to compounds which are CB_1/CB_2 receptor ligands, pharmaceutical compositions containg these compounds, manufacturing processes thereof and uses thereof, and more particularly to compounds that are CB_1/CB_2 receptor agonists. The present invention may also relate to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, vision and/or eye related disorders, gastrointestinal disorders and cardiavascular disorders.

2. Discussion of Relevant Technology

Pain management has been an important field of study for many years. It has been well known that cannabinoid receptor (e.g., CB_1 receptors, CB_2 receptors) ligands, especially agonists produce relief of pain in a variety of animal models by interacting with CB_1 and/or CB_2 receptors. Generally, CB_1 receptors are located predominately in the central nervous system, whereas CB_2 receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While the conventional CB_1 receptor agonists and CB_1/CB_2 receptor agonists, such as tetrahydrocannabinol (THC) and opiate drugs, are highly effective in anti-nociception models in animals, they tend to exert many undesired CNS (central nerve system) side-effects, e.g., psychoactive side effects and the abuse potential of opiate drugs.

Therefore, there is a need for new CB_1/CB_2 receptor ligands such as agonists useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects. The compounds of the invention may be used to avoid the undesired CNS side effects which arise through the central CB1 mechanism.

DISCLOSURE OF THE INVENTION

The present invention provides CB_1/CB_2 receptor ligands which are useful in treating pain and other related symptoms or diseases.

Definitions

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures. Optionally, a name of a compound may be generated using a chemical naming program: ACD/ChemSketch, Version 5.09/September 2001, Advanced Chemistry Development, Inc., Toronto, Canada.

"CB_1/CB_2 receptors" means CB_1 and/or CB_2 receptors.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms, and having 0 to n multivalent heteroatoms selected from O, S, N and P, wherein m and n are 0 or positive integers, and n>m. For example, "C_{1-6}" would refer to a chemical group having 1 to 6 carbon atoms, and having 0 to 6 multivalent heteroatoms selected from O, S, N and P.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" general includes both saturated alkyl and unsaturated alkyl.

The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms.

The term "arylene" used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to links two structures together.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-

containing structure or molecule has an aromatic character (*e.g.*, 4n + 2 delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character.

The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more C_{1-12}hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include heterocyclyl, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C_{1-12}hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

The term "optionally substituted" refers to both groups, structures, or molecules that are substituted and those that are not substituted.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline,

tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl,

phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term “alkoxy” used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein -R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

The term "aryloxy" used alone or as suffix or prefix, refers to radicals of the general formula –O-Ar, wherein -Ar is an aryl.

The term "heteroaryloxy" used alone or as suffix or prefix, refers to radicals of the general formula –O-Ar', wherein -Ar' is a heteroaryl.

The term “amine” or “amino” used alone or as a suffix or prefix, refers to radicals of the general formula –NRR’, wherein R and R’ are independently selected from hydrogen or a hydrocarbon radical.

"Acyl" used alone, as a prefix or suffix, means –C(=O)-R, wherein -R is an optionally substituted hydrocarbyl, hydrogen, amino or alkoxy. Acyl groups include, for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

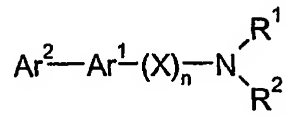
"RT" or "rt" means room temperature.

A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms therebetween.

"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

Description of Preferred Embodiments

In one aspect, the invention provides a compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

Ar^1 is arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar^1 connected to Ar^2 is seperated from a ring atom of Ar^1 connected to X by at least one atom;

Ar^2 is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

n is 0 or 1;

X is a divalent group that separates groups connected thereto by one or two atoms;

R^1 is a monovalent C_{1-20} group comprising one or more heteroatoms selected from S, O, N and P;

R^2 is hydrogen, C_{1-10} alkyl, C_{1-10}acyl, substituted C_{1-10}acyl, substituted C_{1-10} alkyl, C_{1-10} alkylene, or substituted C_{1-10} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

Particularly, the compounds of the present invention are those of formula I, wherein

Ar^1 is an arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar^1 connected to Ar^2 is seperated from a ring atom of Ar^1 connected to X by at least one atom;

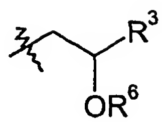
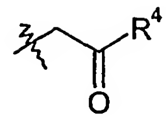
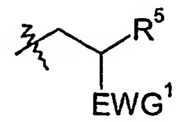
Ar^2 is an aryl, heteroaryl, substituted aryl or substituted heteroaryl;

X is $-CH_2-$, or $-CH_2-CH_2-$;

R^2 is C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{1-3} alkylene, or substituted C_{1-3} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

More particularly, the compounds of the present invention are those of formula I, wherein

R^1 is selected from:

 ,  , and  ;

wherein R^3 is optionally hydrogen, substituted C_{1-10}alkyl, optionally substituted C_{5-12}aryl, optionally substituted C_{3-10}heteroaryl, optionally substituted aryloxy-C_{1-6}alkyl, optionally substituted heteroaryloxy-C_{1-6}alkyl;

R^4 and R^5 are, independently, hydrogen, optionally substituted C_{1-10}alkyl, optionally substituted C_{5-12}aryl, optionally substituted C_{3-10}heteroaryl, amino group, -NHC(=O)-O-R^7, or -NHC(=O)-R^7, wherein R^7 is C_{1-6}alkyl or aryl;

R^6 is hydrogen, optionally substituted C_{1-6}alkyl, or optionally substituted aryl; and

EWG^1 is an electron withdrawing group.

Even more particularly, the compounds of the present invention are those of formula I, wherein

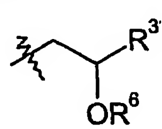
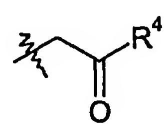
Ar^1 is optionally substituted *para*-phenylene, optionally substituted six-membered *para*-heteroarylene, or optionally substituted monocyclic five-membered *meta*-heteroarylene;

Ar^2 is optionally substituted phenyl, or optionally substituted monocylic five or six-membered heteroaryl;

X is $-CH_2$-, or $-CH_2-CH_2$-;

R^2 is C_{1-3} alkyl, substituted C_{1-3} alkyl, C_{1-3} alkylene, or substituted C_{1-3} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

R^1 is selected from:

 , and  ,

wherein R^3 is optionally substituted C_{1-6}alkyl, optionally substituted phenyl, optionally substituted phenoxy-methyl;

R^4 is, independently, optionally substituted C_{1-6}alkyl, optionally substituted phenyl, amino, -NHC(=O)-O-R^7, or -NHC(=O)-R^7, wherein R^7 is C_{1-6}alkyl or phenyl; and

R^6 is hydrogen, methyl or ethyl.

Most particularly, the compounds of the present invention are those of formula I, wherein

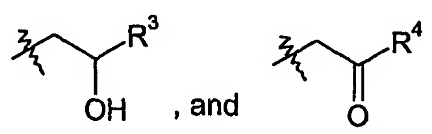
Ar^1 is *para*-phenylene or *para*-pyridylene;

Ar^2 is a phenyl *ortho*-substituted with an electron withdrawing group, or a thienyl *ortho*-substituted with an electron withdrawing group; Even more particularly, Ar^2 is a phenyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, -O-$CH(CH_3)_2$, $-CF_3$, $-NO_2$, or -CN; or thienyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, -O-$CH(CH_3)_2$, $-CF_3$, $-NO_2$, -CN, wherein said *ortho*-substituted Ar^2 is optionally further substituted at its non-*ortho* position;

X is $-CH_2-$;

R^2 is methyl.

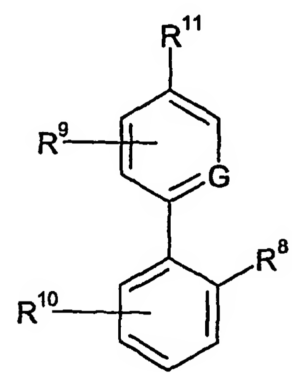
R^1 is selected from:



wherein R^3 is optionally substituted phenyl, or optionally substituted phenoxy-methyl; Even more particularly, R^3 is phenyl, substituted phenoxymethyl or substituted phenyl; and

R^4 is $-NHC(=O)-O-R^7$, wherein R^7 is C_{1-6}alkyl.

In another aspect, the present invention provides a compound of formula II, or a pharmaceutically acceptable salt thereof:



II

wherein

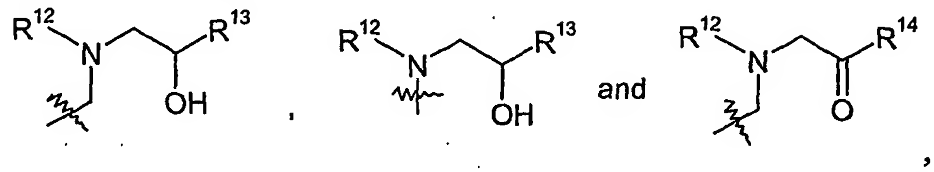
G is N or CH;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

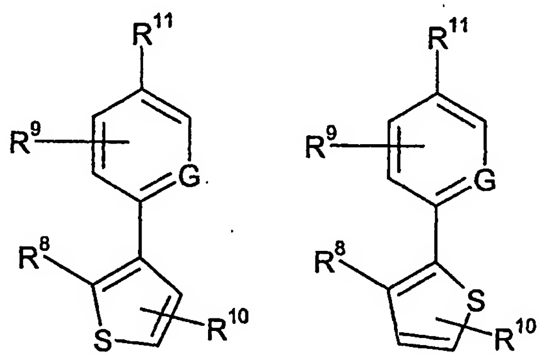
R^{10} is selected from –H and C_{1-3}alkyl; and

R^{11} is selected from



wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxymethyl, R^{14} is $-NHC(=O)OR^{15}$, wherein R^{15} is C_{1-6}alkyl.

In a further aspect, the present invention provides a compound of formula III or IV, or a pharmaceutically acceptable salt thereof:



III IV

wherein

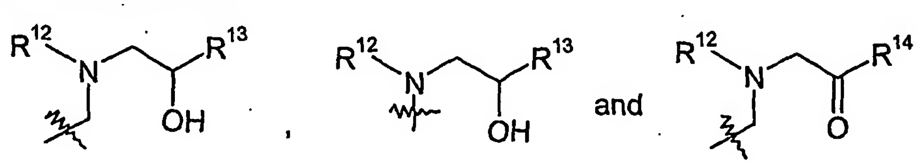
G is N or CH;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

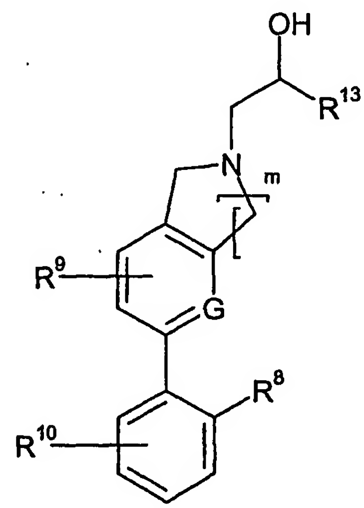
R^{10} is selected from –H and C_{1-3}alkyl; and

R^{11} is selected from



wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxymethyl, R^{14} is $-NHC(=O)OR^{15}$, wherein R^{15} is C_{1-6}alkyl.

In an even further aspect, the present invention provides a compound of formula V, or a pharmaceutically acceptable salt thereof:



V

wherein

G is N or CH;

m is 1 or 2;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

R^{10} is selected from –H and C_{1-3}alkyl; and

R^{13} is phenyl or substituted phenoxymethyl.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I, II, III, IV or V. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present

invention includes any geometrical isomer of a compound of Formula I, II, III, IV or V. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I, II, III, IV or V.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I, II, III, IV or V.

Within the scope of the invention are also salts of the compounds of the formula I, II, III, IV or V. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of formula I, II, III, IV or V above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB_1/CB_2 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB_1/CB_2 receptors, and are useful in the relief of pain, particularly chronic pain, e.g., chronic inflammatory pain, neuropathic pain, back pain, cancer pain and visceral pain. Compounds of the present invention will also be useful in treating acute pain. Additionally, compounds of the present invention are useful in other disease states in which degeneration or dysfunction of CB_1/CB_2 receptors is present or implicated.

Thus, the invention provides a compound of formula I, II, III, IV or V, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula I, II, III, IV or V, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be contrued accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I, II, III, IV or V as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I, II, III, IV or V for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I, II, III, IV or V for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I, II, III, IV or V above, is administered to a patient in need of such therapy.

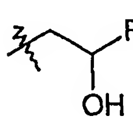
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

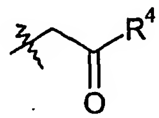
Further, there is provided a pharmaceutical composition comprising a compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

In a further aspect, the present invention provides a method of preparing a compound of the present invention using one or more of the general procedures

below, wherein R_a and R_b are independently selected from –H, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl, -CF_3, -NO_2, and –CN; n is 1 or 2; R_c, R_d, R_e and R_f are independently selected from –H, C_{1-3}alkyl,



, and

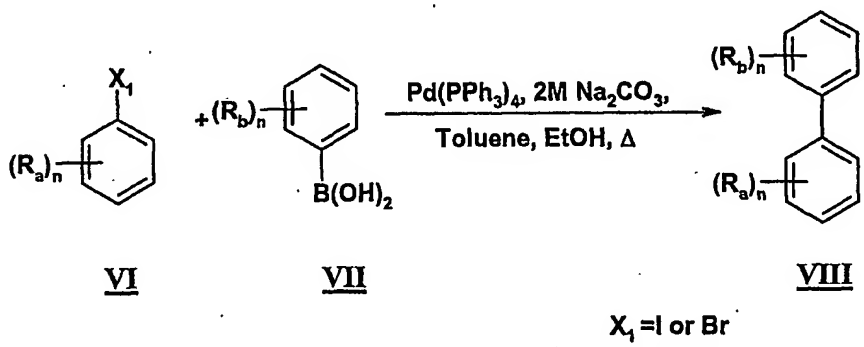


,

wherein R^3 is optionally substituted phenyl, or optionally substituted phenoxymethyl;

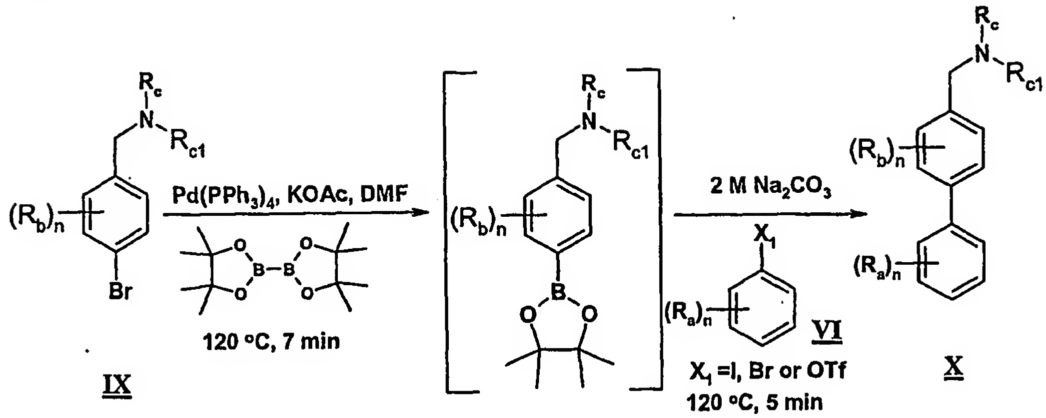
R^4 is -NHC(=O)-O-R^7, wherein R^7 is C_{1-6}alkyl; R_{c1} is –H or C_{1-3}alkyl; and R_g is optionally subsitituted phenyl or optionally subsituted phenoxymethyl.

General Procedure 1:



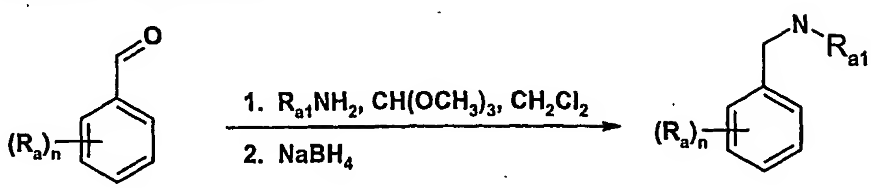
A solution of the aryl boronic acid (VII, 1.5 equiv.) in ethanol (3 mL/mmol boronic acid) was added to a mixture of the aryl halide (VI, 1 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), toluene (9 mL/mmol aryl halide), and 2 M Na_2CO_3 (6.7 equiv.). The resulting mixture was heated at reflux until the aryl halide was consumed (typically 16 h). The reaction was then concentrated *in vacuo*, and the residue was diluted with water. The aqueous phase was extracted with EtOAc (3x). The combined organic phases were then washed with brine, dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The residue was dissolved in methanol and allowed to stand overnight. The orange solid which precipitated was filtered, and the supernatant was concentrated *in vacuo* to provide the title compound. The product (VIII) was used for subsequent steps, or purified by silica gel column chromatography when necessary.

General Procedure 2:



Solutions of the aryl bromide (IX, 1 equiv.) in DMF (3 mL/mmol aryl bromide) and bis(pinacolato)diboron (1.1 equiv.) in DMF (2.7 mL/mmol diboron compound) were added successively to a mixture of $Pd(PPh_3)_4$ (0.03 equiv.) and KOAc (3 equiv.) contained in a microwave process vial. The vial was capped and heated to 120 °C for 7 min using microwave irradiation. The resulting mixture was cooled, and 2 M Na_2CO_3 (4.9 equiv.) and a solution of the second aryl halide or aryl triflate (VI, 1-2 equiv.) in DMF (0.3-0.9 mL/mmol aryl halide/triflate, depending on solubility) were added to the vial through the septum cap. The reaction was heated to 120 °C for an additional 5 minutes using microwave irradiation. The resulting mixture was diluted with water (6 mL/mmol of initial aryl halide used) and CH_2Cl_2 (24 mL/mmol of initial aryl halide used), loaded onto an Extube® Chem Elut column (Varian), and eluted with two column volumes of CH_2Cl_2. The eluant was concentrated, and the residue was dissolved in CH_2Cl_2 (12 mL/mmol of initial aryl halide used). MP-TsOH resin was added to the solution, and the mixture was stirred for 2 hours. The resin was removed by filtration and washed with additional CH_2Cl_2 and MeOH. The filtrate and washings were discarded, and the compound (X) was then released from the resin using 2M NH_3 in MeOH. The release solution was concentrated to provide the compound (X).

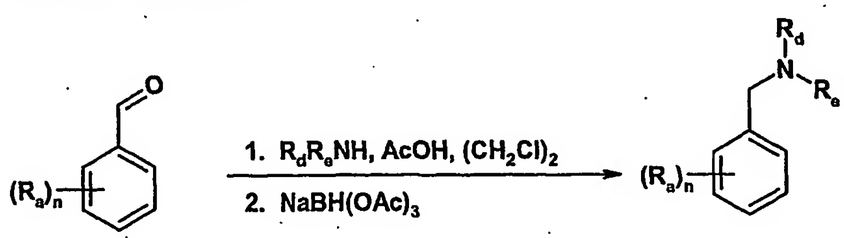
General Procedure 3:



XI XII

A solution of $R_{a1}NH_2$ in MeOH (2 M, 5 equiv.) was added to a mixture of the aldehyde (XI, 1 equiv.) and $CH(OCH_3)_3$ (10 equiv) in CH_2Cl_2 (7.5 mL/mmol aldehyde). The resulting mixture was stirred overnight at room temperature, and then $NaBH_4$ (2.5 equiv.) was added. When the starting aldehyde/intermediate imine had been completely consumed, the reaction was concentrated *in vacuo*. The residue was taken into EtOAc (10 mL/mmol aldehyde used) and the product was extracted into 1 N HCl (3 x 7.5 mL/mmol aldehyde used). The EtOAc layer was discarded, the combined aqueous layers were basicified with 6 N NaOH, and the product was back extracted with EtOAc (3 x 10 mL/mmol aldehyde used). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the compound (XII). The compound (XII) was used for subsequent steps, or purified by silica gel column chromatography when necessary.

General Procedure 4:

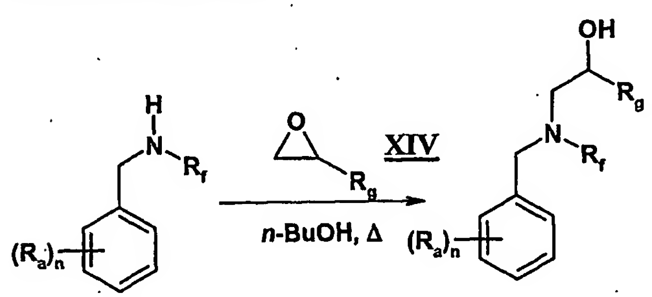


XI XIII

A solution of the amine (R_dR_eNH, 1 equiv.) and aldehyde (XI, 1-2 equiv.) in AcOH/dichloroethane (5% v/v, 10 mL/mmol amine) was stirred at room temperature overnight. $NaBH(OAc)_3$ (2 equiv.) was then added. When the starting aldehyde/intermediate imine/iminium ion had been completely consumed, saturated Na_2CO_3 (6 mL/mmol amine) was added. The layers were separated, and the aqueous

layer was extracted with additional EtOAc (3 x 12 mL/mmol amine). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the compound (XIII). The compound (XIII) was used for subsequent steps, or purified by silica gel column chromatography or reverse phase HPLC when necessary.

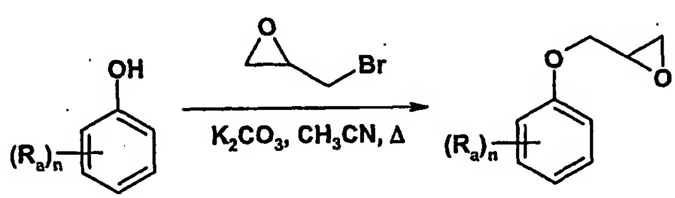
General Procedure 5:



XII XV

A solution of the amine (XII, 1 equiv.) and epoxide (XIV, 1 equiv.) in *n*-BuOH (6 mL/mmol amine) was heated at the temperature specified until the starting materials were consumed. The reaction was concentrated *in vacuo*, and the residue was purified by reverse phase HPLC to provide the compound (XV).

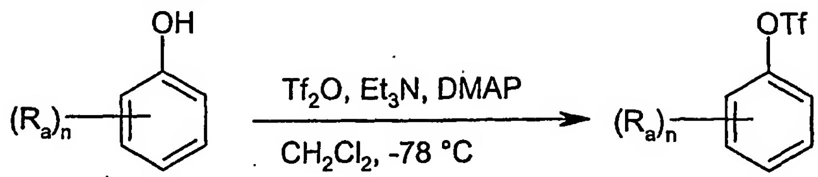
General Procedure 6:



XVI XVII

A suspension of the phenol (XVI, 1 equiv.), epibromohydrin (5 equiv.), and K_2CO_3 (5 equiv.) in dry CH_3CN (8 mL/mmol phenol) was heated at 70 °C until the starting phenol was completely consumed (typically 16 h). The reaction mixture was filtered to remove solids which were then washed with additional CH_3CN. The filtrate was concentrated to provide the compound (XVII).

General Procedure 7:



XVI XVIII

Triethylamine (2.2 equiv.), followed by triflic anhydride (1.1 equiv.), was added dropwise to a solution of the phenol (XVI, 1 equiv.) and DMAP (0.1 equiv.) in dry CH_2Cl_2 (10 mL/mmol phenol) maintained at –78°C. The reaction was allowed to slowly warm to room temperature and stirred until the starting phenol was completely consumed (typically 16 h). Once the reaction was complete, water was added (10 mL/mmol phenol), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL/mmol phenol). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography on the organic phase residue provided the compound (XVIII).

The compounds of the invention were found to be active towards CB_1/CB_2 receptors in warm-blooded animal, e.g., human. Particularly the compounds of the invention have been found to be effective CB_1/CB_2 receptor agonists. *In vitro* assays, *infra*, demonstrated these surprising activities. In these *in vitro* assays, a compound is tested for their activity toward CB_1/CB_2 receptors and the dissociation constant (Ki) is obtained to determine the selective activity for a particular compound towards CB_1/CB_2 receptors by measuring IC_{50} of the compound. In the current context, IC_{50} generally refers to the concentration of the compound at which 50% displacement of a standard radioactive CB_1/CB_2 receptor ligand has been observed. Generally, a lower Ki for a particular compound towards CB_1/CB_2 receptors means that the particular compound is a stronger ligand towards the CB_1/CB_2 receptors. As a result, compounds with relatively low Ki towards CB_1/CB_2 receptors are relatively strong CB_1/CB_2 receptor ligands or strong CB_1/CB_2 receptor agonists.

Biological Evaluation

<u>hCB_1 and hCB_2 receptor binding</u>

Human CB_1 receptor from Receptor Biology (hCB1) or human CB_2 receptor from BioSignal (hCB2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC_{50} of the compounds of the invention at hCB_1 and hCB_2 are evaluated from 10-point dose-response curves done with ^{3}H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$Ki = IC_{50}/(1+[rad]/Kd),$$

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

Biological data for certain compounds of the invention are listed in Table 1 below.

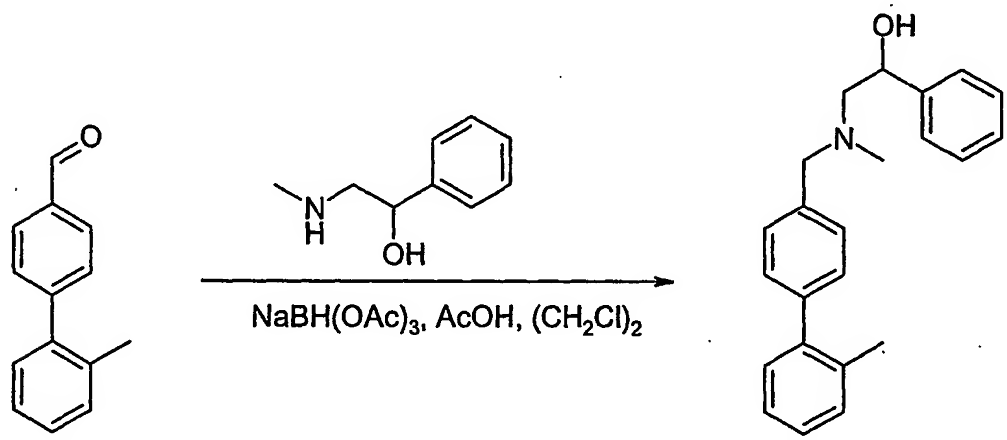
Table 1

Compound No.	CB_2 (Ki, nM)	CB_1 (Ki, nM)
1-132	15-2800	50-5000

EXAMPLES

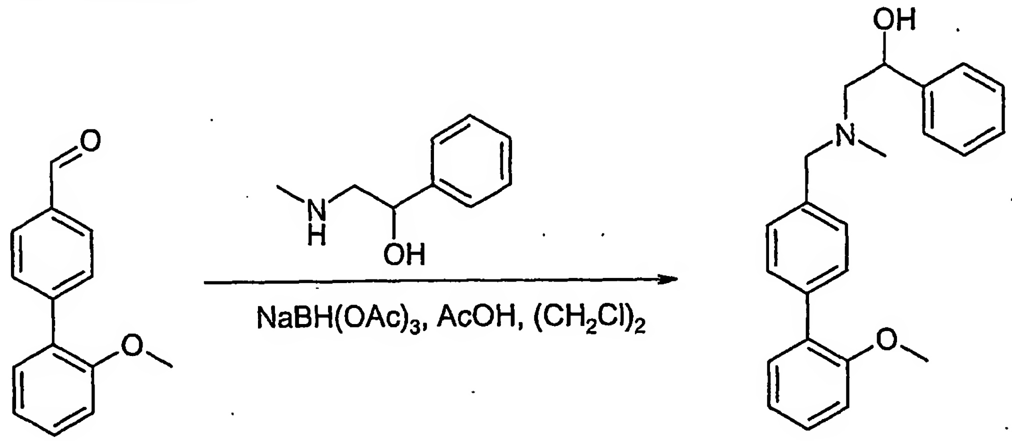
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1: α-[[Methyl[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol



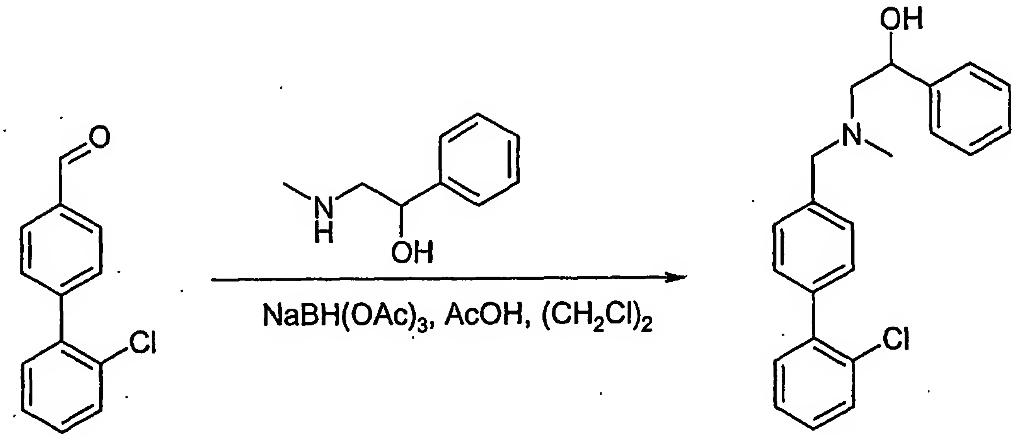
Following General Procedure 4, 2'-methyl-[1,1'-biphenyl]-4-carboxaldehyde (0.250 g, 1.28 mmol), α-[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and $NaBH(OAc)_3$ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmol amine) was added. The layers were then filtered through a Hydromatrix®column and the product was eluted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH_3CN in H_2O) to provide the title compound (0.052 g, 11%) as its HCO_2H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR ($CDCl_3$): δ 7.39-7.23 (br m, 13H), 4.83 (dd, *J*=3.8 Hz, *J*=10.2 Hz, 1H), 3.94-3.85 (overlapping br s at 3.94 and d at 3.87, *J*=13.2 Hz, 2H), 3.68 (d, *J*=12.8 Hz, 1H), 2.72 (dd, *J*=10.0 Hz, *J*=12.4 Hz, 1H), 2.63 (dd, *J*=3.6 Hz, *J*=12.0 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H). MS (ESI) $(M+H)^+ = 332$. Anal. Calcd for $C_{23}H_{25}NO$ + 0.30 CH_2O_2: C, 81.06; H, 7.47; N, 4.06. Found: C, 81.40; H, 7.76; N, 4.18.

Example 2: α-[[[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol



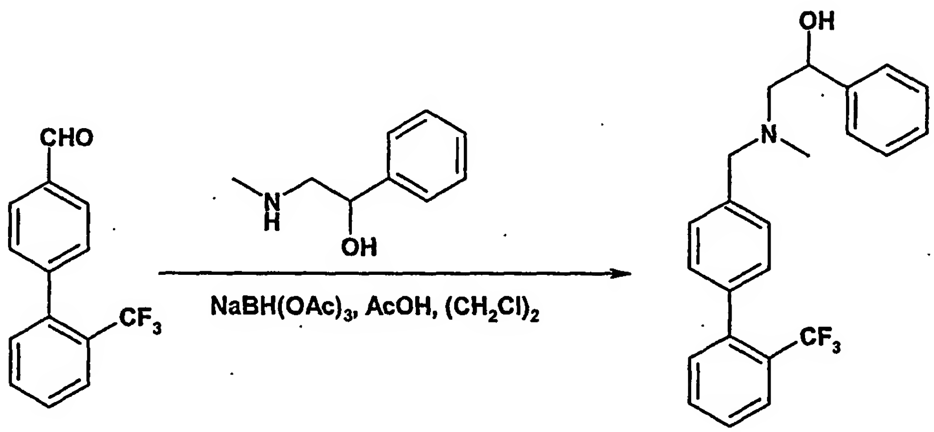
Following General Procedure 4, 2'-methoxy-[1,1'-biphenyl]-4-carboxaldehyde (0.250 g, 1.18 mmol), α-[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and $NaBH(OAc)_3$ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmol amine) was added. The layers were then filtered through a Hydromatrix® column and the product was eluted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH_3CN in H_2O) to provide the title compound (0.048 g, 10%) as its HCO_2H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR ($CDCl_3$): δ 7.54 (d, J=8.4 Hz, 2H), 7.40-7.25 (br m, 9H), 7.05-6.98 (m, 2H), 4.88 (dd, J=2.6 Hz, J=10.2 Hz, 1H), 4.55 (br s, 1H), 3.91 (d, J=13.6 Hz, 1H), 3.81-3.74 (overlapping s at 3.81 and d at 3.75, J=13.2 Hz, 4H), 2.79 (dd, J=10.0 Hz, J=13.2 Hz, 1H), 2.68 (dd, J=3.2 Hz, J=12.8 Hz, 1H), 2.48 (s, 3H). MS (ESI) $(M+H)^+$ = 348. Anal. Calcd for $C_{23}H_{25}NO_2$ + 0.40 CH_2O_2: C, 76.82; H, 7.11; N, 3.83. Found: C, 76.98; H, 7.17; N, 3.77.

Example 3: α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol



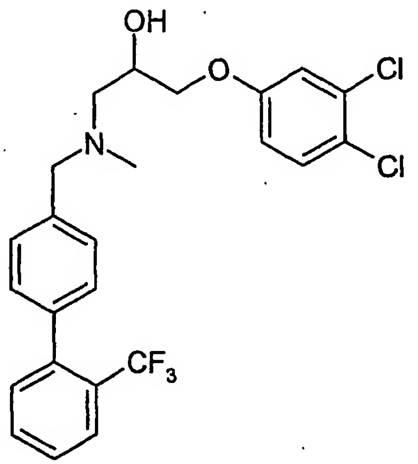
Following General Procedure 4, 2'-chloro-[1,1'-biphenyl]-4-carboxaldehyde (0.250 g, 1.16 mmol), α-[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and $NaBH(OAc)_3$ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmol amine) was added. The layers were then filtered through a Hydromatix® column and the product was eluted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH_3CN in H_2O) to provide the title compound (0.050 g, 11%) as its HCO_2H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR ($CDCl_3$): δ 7.49-7.26 (br m, 13H), 4.85 (dd, *J*=3.2 Hz, *J*=10.8 Hz, 1H), 4.18 (br s, 1H), 3.89 (d, *J*=12.8 Hz, 1H), 3.72 (d, *J*=13.2 Hz, 1H), 2.75 (dd, *J*=10.4 Hz, *J*=12.8 Hz, 1H), 2.65 (dd, *J*=3.2 Hz, *J*=12.8 Hz, 1H), 2.46 (s, 3H). MS (ESI) $(M+H)^+$ = 352. Anal. Calcd for $C_{22}H_{22}NOCl$ + 0.30 CH_2O_2: C, 73.25; H, 6.23; N, 3.83. Found: C, 73.44; H, 6.31; N, 3.86.

Example 4: α-[[Methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol

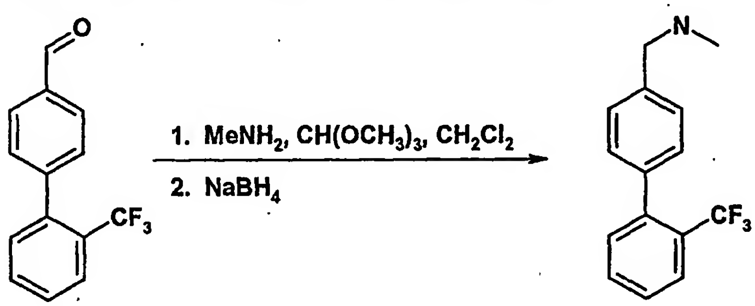


Following General Procedure 4, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.500 g, 2.00 mmol), α-[(methylamino)methyl]benzenemethanol (0.604 g, 4.00 mmol), and $NaBH(OAc)_3$ (0.844 g, 4.00 mmol) were combined. The crude product was purified by flash chromatography (3:7 Hexanes:EtOAc) to provide the title compound. HCl in Et_2O (2 mL of 1M, 2.00 mmol) was added to the compound and the resulting solid was filtered and washed with additional Et_2O to provide the HCl salt (0.558 g, 66%). Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.81 (d, J=7.6 Hz, 1H), 7.71-7.56 (m, 4H), 7.52-7.32 (m, 8H), 5.15-5.09 (m, 1H), 4.77 (br d, J=14.0 Hz, 0.5H), 4.50 (AB_q, 1H), 4.33 (br d, J=12.0 Hz, 0.5H), 3.46-3.15 (m, 2H), 3.08 (s, 1.5H), 2.92 (s, 1.5H). MS (ESI) $(M+H)^+$ = 386. Anal. Calcd for $C_{23}H_{22}F_3NO$+1.1 HCl: C, 64.92; H, 5.47; N, 3.29. Found: C, 65.16; H, 5.63; N, 3.37.

Example 5: 1-(3,4-Dichlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol

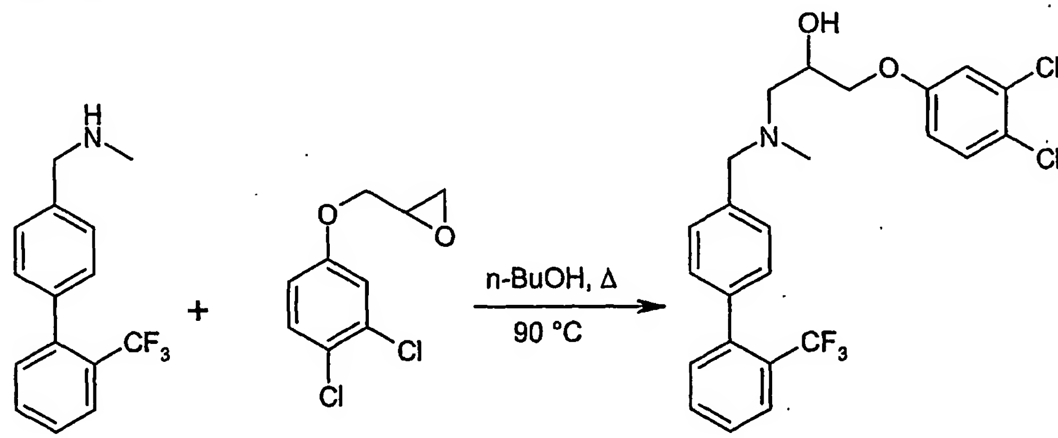


Compound 5A: ***N*-Methyl-2'-(trifluoromethyl)- [1,1'-biphenyl]-4-methanamine**



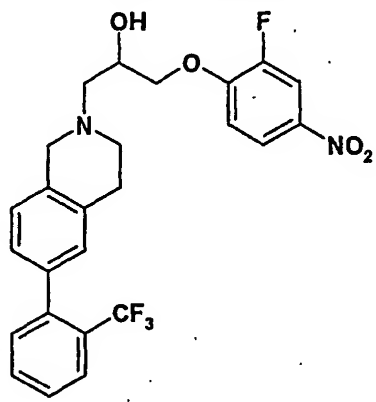
Following General Procedure 3, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.400 g, 1.60 mmol) was converted to the title compound (0.297 g, 70%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$) δ 7.75 (d, *J*=7.6 Hz, 1H), 7.56 (t, *J*=7.2 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.42-7.28 (m, 5H), 3.82 (s, 2H), 2.51 (s, 3H), 2.13 (br s, 1H). MS (ESI) $(M+H)^+ = 266$.

Compound 5b: 1-(3,4-Dichlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol

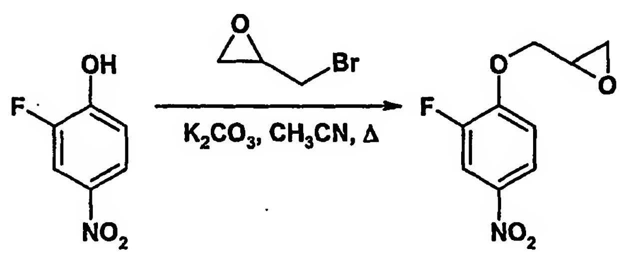


Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.133 g, 0.40 mmol) and 2-[(3,4-dichlorophenoxy)methyl]oxirane (0.088 g, 0.40 mmol) were combined and heated at 50°C for 24 h. The crude product was purified by reverse phase HPLC (gradient 30-70% CH_3CN in H_2O) to provide the title compound (0.026 g, 11%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.77 (d, *J*=7.6 Hz, 1H), 7.60 (t, *J*=7.4 Hz, 1H), 7.53-7.51 (m, 3H), 7.43 (d, *J*=8.0 Hz, 2H), 7.34-7.31 (overlapping s at 7.33 and d at 7.32, *J*=8.8 Hz, 2H), 6.97 (d, *J*=2.8 Hz, 1H), 6.73 (dd, *J*=2.8 Hz, *J*=8.8 Hz, 1H), 4.50 (br s, 1H), 4.36 (br s, 2H), 4.07 (br s, 1H), 3.89 (t, *J*=8.2 Hz, 1H), 3.51-3.03 (br s at 3.36 and br s at 3.16, 2H), 2.94 (br s, 3H). MS (ESI) $(M+H)^+$ = 484. Anal. Calcd for $C_{24}H_{22}Cl_2F_3NO_2$ + 0.3 H_2O + 0.9 TFA: C, 52.31; H, 4.00; N, 2.36. Found: C, 52.32; H, 3.93; N, 2.24.

Example 6: α-[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol

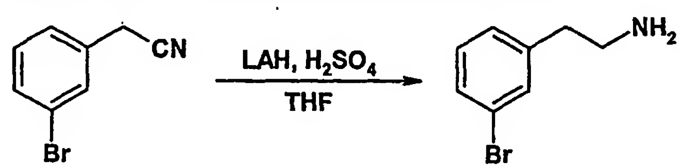


Compound 6a: 2-[(2-Fluoro-4-nitrophenoxy)methyl]oxirane



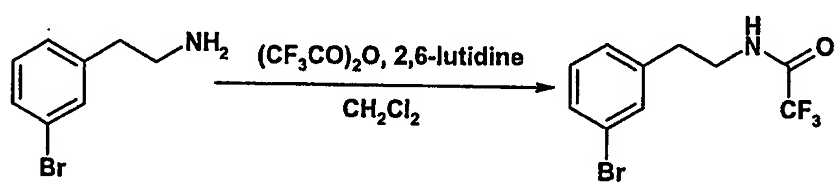
Following General Procedure 6, 2-fluoro-4-nitrophenol (0.471 g, 3.00 mmol) was converted to the title compound (0.635 g, 99%). The crude compound was used for subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 8.06 (ddd, *J*=1.2 Hz, *J*=2.4 Hz, *J*=8.8 Hz, 1H), 8.00 (dd, *J*=2.4 Hz, *J*=10.4 Hz, 1H), 7.10 (dd, *J*=8.0 Hz, *J*=9.2 Hz, 1H), 4.48 (dd, *J*=2.4 Hz, *J*=11.2 Hz, 1H), 4.11 (dd, *J*=6.0 Hz, *J*=11.6 Hz, 1H), 3.45-3.39 (m, 1H), 2.97 (dd, *J*=4.0 Hz, *J*=4.8 Hz, 1H), 2.81 (dd, *J*=2.8 Hz, *J*=4.8 Hz, 1H).

Compound 6b: 3-Bromobenzeneethanamine



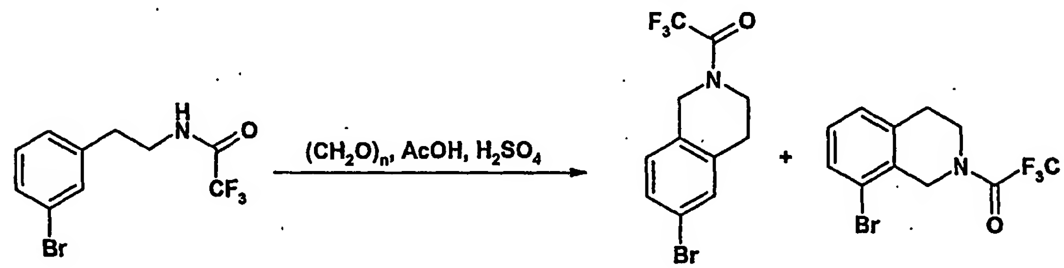
A suspension of $LiAlH_4$ (1.24 g, 32.7 mmol) in dry THF (50 mL) was cooled to 0 °C. Concentrated H_2SO_4 (1.6 g, 16.3 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 min. A solution of 3-bromo-benzeneacetonitrile (4.01 g, 20.4 mmol) in THF (5 mL) was added dropwise, and the reaction was allowed to warm to room temperature when the addition was complete. The reaction was stirred at room temperature for 1h, and then cooled back to 0 °C and quenched by the addition of a 1:1 THF:H_2O mixture (5 mL). Et_2O was added (20 mL), followed by a 3.6 M solution of NaOH (10 mL). The mixture was filtered through Celite, and the solids were washed well with additional Et_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (3.91 g, 96%). The crude compound was used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.38-7.30 (overlapping s at 7.35 and d, *J*=7.2 Hz for d, 2H), 7.20-7.10 (m, 2H), 2.96 (t, *J*=6.8 Hz, 2H), 2.72 (t, *J*=6.4 Hz, 2H), 1.35 (br s, 2H). MS (ESI) $(M+H)^+$ = 200/202.

Compound 6c: ***N*-[2-(3-Bromophenyl)ethyl]-2,2,2-trifluoroacetamide**



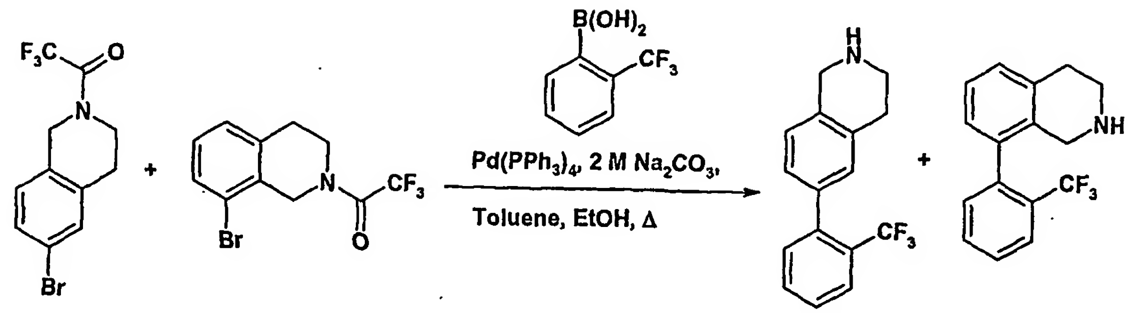
A mixture of 3-bromobenzeneethanamine (2.00 g, 10.0 mmol) and 2,6-lutidine (1.2 mL, 10.3 mmol) in dry CH_2Cl_2 (40 mL) was cooled to 0 °C. Trifluoroacetic anhydride (1.4 mL, 9.9 mmol) was added dropwise, and the reaction was then warmed to room temperature and allowed to stir for 16 h. Water (40 mL) was added to the reaction, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic phases were washed successively with 1 M HCl (40 mL) and saturated $NaHCO_3$ (40 mL), and then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (2.93 g, 100%). The crude compound was used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.40 (d, *J*=8.0 Hz, 1H), 7.36 (s, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 7.12 (d, *J*=7.6 Hz, 1H), 6.33 (br s, 1H), 3.59 (q, *J*=6.8 Hz, 2H), 2.87 (t, *J*=7.2 Hz, 2H). MS (ESI) $(M+H)^+$ = 296/298.

Compound 6d: 6-Bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline and 8-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline



A mixture of glacial acetic acid (22.5 mL) and concentrated sulfuric acid (15 mL) was added to a mixture of *N*-[2-(3-bromophenyl)ethyl]-2,2,2-trifluoroacetamide (4.06 g, 13.7 mmol) and paraformaldehyde (0.659 g, 22.0 mmol equiv. of formaldehyde). The reaction was stirred at room temperature for 16 h, and then poured into 300 mL of cold water. The aqueous solution was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ (75 mL) and water (2 x 150 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide a mixture of the title compounds (3.31 g, 78%). Due to hindered rotation about the amide bond, rotamers were observed in the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): δ 7.46 (dd, *J*=2.0 Hz, *J*=6.8 Hz, 0.33H), 7.38-7.31 (m, 1.33H), 7.15-7.09 (m, 0.67H), 7.05-6.98 (m, 0.67H), 4.75, 4.73, 4.69 (3 x s, 2H), 3.90-3.80 (m, 2H), 3.00-2.90 (m, 2H). MS (ESI) $(M+H)^+$ = 308/310.

Compound 6e: 1,2,3,4-Tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline and 1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline

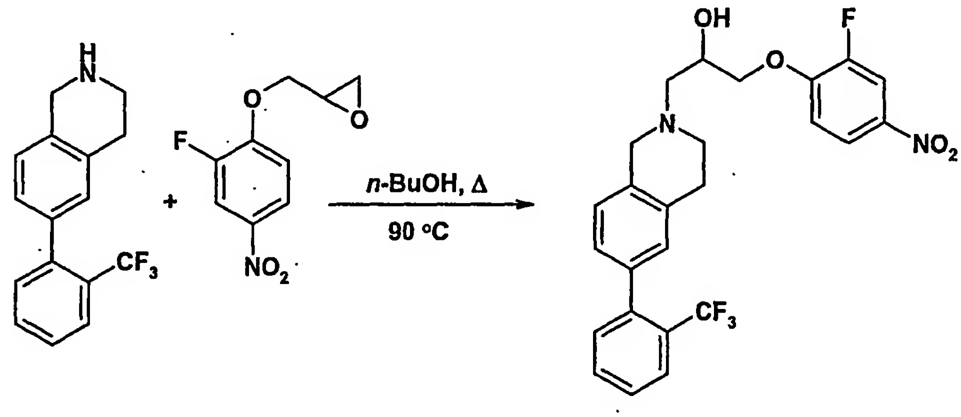


Following General Procedure 1, a mixture of 6-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline and 8-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)-isoquinoline (0.137 g, 0.446 mmol) was reacted with [2-(trifluoromethyl)phenyl]-boronic acid (0.127 g, 0.668 mmol) to provide a mixture of the title compounds. Purification by column chromatography (4:1 CH_2Cl_2:MeOH + 0.1% conc. NH_3) provided 1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline (0.0380 g, 31%) and 1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline (0.0810 g, 65%).

1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline: ^{1}H-NMR ($CDCl_3$): δ 7.77 (d, J=7.2 Hz, 1H), 7.56 (t, J=7.6 Hz, 1H), 7.49 (t, J=7.6 Hz, 1H), 7.23 (d, J=7.6 Hz, 1H), 7.21 (t, J=7.6 Hz, 1H), 7.16 (d, J=6.8 Hz, 1H), 7.01 (d, J=7.6 Hz, 1H), 4.66 (br s, 1H), 3.72 (half of br AB_q, J=16.0 Hz, 1H), 3.57 (half of br AB_q, J=15.6 Hz, 1H), 3.19 (br s, 2H), 2.97 (br s, 2H). MS (ESI) $(M+H)^+$ = 278.

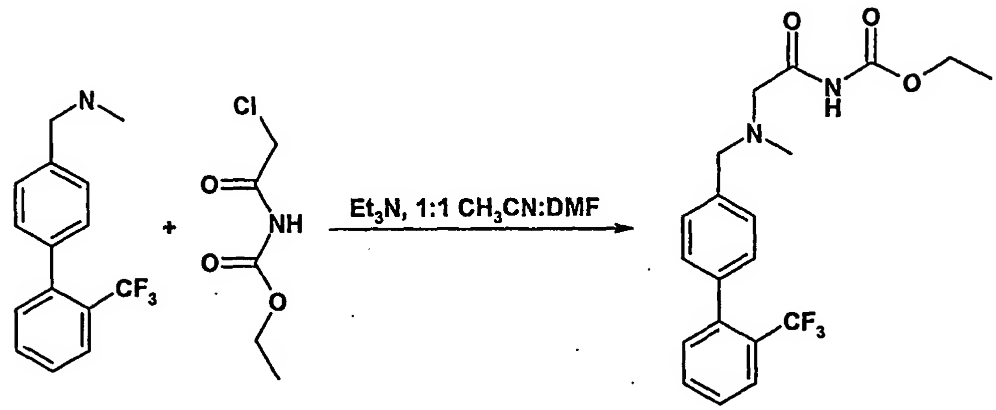
1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline: ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, J=7.6 Hz, 1H), 7.55 (t, J=6.8 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.12 (d, J=8.4 Hz, 1H), 7.07 (s, 1H), 7.06 (d, J=8.0 Hz, 1H), 4.12 (br s, 2H), 3.87 (br s, 1H), 3.23 (br s, 2H), 2.88 (br s, 2H). MS (ESI) $(M+H)^+$ = 278.

Compound 6f: α-[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol



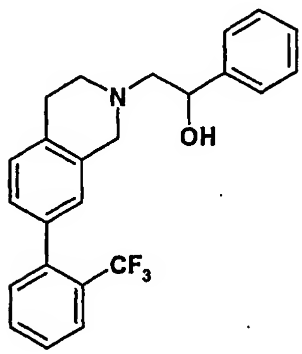
Following General Procedure 5, 1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]-isoquinoline (0.0256 g, 0.0923 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]-oxirane (0.0197 g, 0.0924 mmol) were combined and heated at 90 °C for 16 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.0222 g, 40%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.15-8.11 (m, 1H), 8.08 (dd, *J*=2.8 Hz, *J*=11.2 Hz, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.39-7.24 (m, 5H), 4.82-4.50 (br m, 3H), 4.29 (d, *J*=4.8 Hz, 2H), 3.95 (br s, 1H), 3.62-3.52 (m, 3H), 3.38-3.22 (br m, 2H). MS (ESI) $(M+H)^+$ = 491. Anal. Calcd for $C_{25}H_{22}F_4N_2O_4$+1.1 TFA+0.7 H_2O: C, 51.98; H, 3.93; N, 4.46. Found: C, 52.02; H, 3.93; N, 4.42.

Example 7: Ethyl [[methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]-acetyl]carbamate

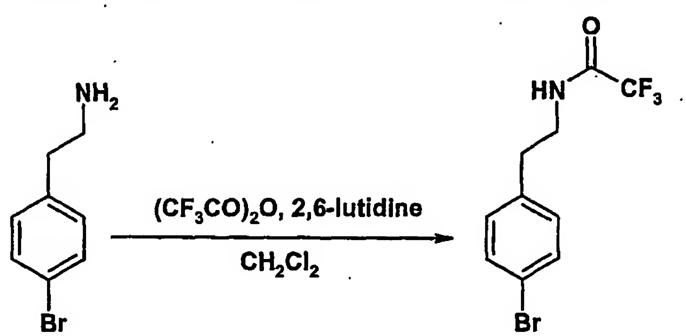


A mixture of N-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.0781 g, 0.294 mmol), ethyl N-(chloroacetyl)carbamate (0.0487 g, 0.294 mmol), and triethylamine (0.041 mL, 0.29 mmol) in 1:1 CH_3CN:DMF (3 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated, and the residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.0992 g, 86%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. ^{1}H-NMR (CD_3OD): δ 7.81 (d, *J*=8.0 Hz, 1H), 7.68 (t, *J*=7.6 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 2H), 7.59 (t, *J*=8.0 Hz, 1H), 7.46 (d, *J*=8.0 Hz, 2H), 7.38 (d, *J*=7.6 Hz, 1H), 4.70-4.30 (br, 3H), 4.24 (q, *J*=7.2 Hz, 2H), 2.95 (s, 3H), 1.31 (t, *J*=7.2 Hz, 3H). MS (ESI) $(M+H)^+$ = 395. Anal. Calcd for $C_{20}H_{21}F_3N_2O_3$+1.3 TFA+0.4 H_2O: C, 49.37; H, 4.23; N, 5.09. Found: C, 49.45; H, 4.23; N, 5.05.

Example 8: 3,4-Dihydro-α-phenyl-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol

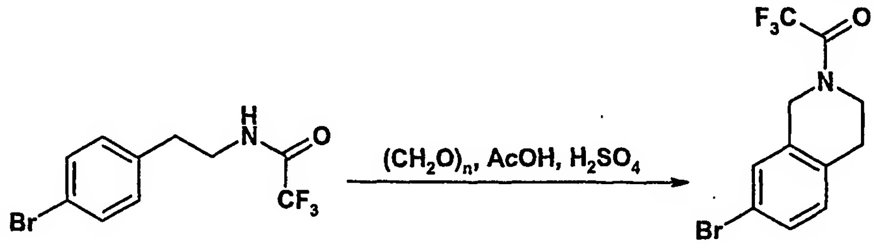


Compound 8a: *N*-[2-(4-Bromophenyl)ethyl]-2,2,2-trifluoroacetamide



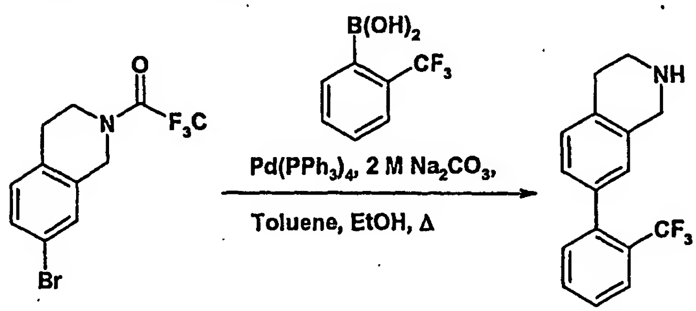
A mixture of 4-bromobenzeneethanamine (1.23 g, 6.17 mmol) and 2,6-lutidine (0.76 mL, 6.5 mmol) in dry CH_2Cl_2 (25 mL) was cooled to 0 °C. Trifluoroacetic anhydride (0.87 mL, 6.2 mmol) was added dropwise, and the reaction was then warmed to room temperature and allowed to stir for 16 h. Water (25 mL) was added to the reaction, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were washed successively with 1 M HCl (25 mL) and saturated $NaHCO_3$ (25 mL), and then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (1.79 g, 98%). The crude compound was used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.49-7.45 (m, 2H), 7.10-7.06 (m, 2H), 6.27 (br s, 1H), 3.61 (q, *J*=6.8 Hz, 2H), 2.86 (t, *J*=6.8 Hz, 2H). MS (ESI) $(M+H)^+$ = 296/298.

Compound 8b: **7-Bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline**



A mixture of glacial acetic acid (5.1 mL) and concentrated sulfuric acid (3.4 mL) was added to a mixture of *N*-[2-(4-bromophenyl)ethyl]-2,2,2-trifluoroacetamide (0.903 g, 3.05 mmol) and paraformaldehyde (0.147 g, 4.88 mmol equiv. of formaldehyde). The reaction was stirred at room temperature for 20 h, and then poured into 65 mL of cold water. The aqueous solution was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with saturated $NaHCO_3$ (16 mL) and water (2 x 35 mL), and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide the title compound (0.885 g, 94%) as a colorless oil. Due to hindered rotation about the amide bond, rotamers were observed in the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): δ 7.38-7.27 (m, 2H), 7.06 (d, *J*=9.6 Hz, 0.36H), 7.04 (d, *J*=8.4 Hz, 0.64H), 4.76 (s, 1.3H), 4.71 (s, 0.7H), 3.88 (t, *J*=6.4 Hz, 0.7H), 3.84 (t, *J*=6.4 Hz, 1.3H), 2.91 (t, *J*=5.6 Hz, 1.3H), 2.90 (t, *J*=6.4 Hz, 0.7H). MS (ESI) $(M+H)^+$ = 308/310.

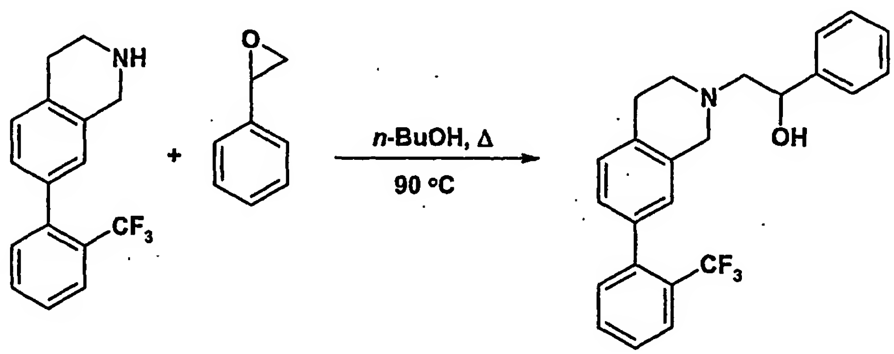
Compound 8c: 1,2,3,4-Tetrahydro-7-[2-(trifluoromethyl)phenyl]isoquinoline



Following General Procedure 1, 7-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline (0.468 g, 1.52 mmol) was reacted with [2-(trifluoromethyl)phenyl]boronic acid (0.433 g, 2.28 mmol) to provide the title compound (0.387 g, 92%) following purification by column chromatography (85:15 CH_2Cl_2:MeOH + 0.1% conc. NH_3). ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, *J*=8.0 Hz, 1H), 7.54

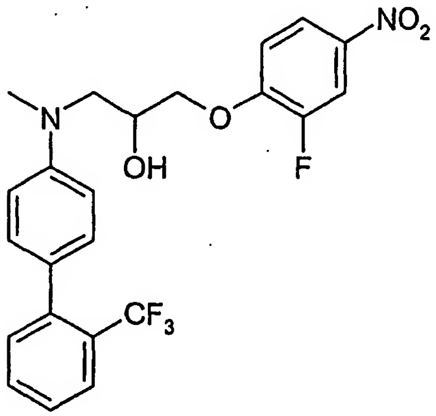
(t, *J*=7.6 Hz, 1H), 7.45 (t, *J*=8.0 Hz, 1H), 7.31 (d, *J*=7.6 Hz, 1H), 7.12 (collapsed AB_q, 2H), 6.99 (s, 1H), 4.05 (s, 2H), 3.20 (t, *J*=5.6 Hz, 2H), 2.86 (t, *J*=6.0 Hz, 2H), 2.43 (br s, 1H). MS (ESI) $(M+H)^+ = 278$.

Compound 8d: 3,4-Dihydro-α-phenyl-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol

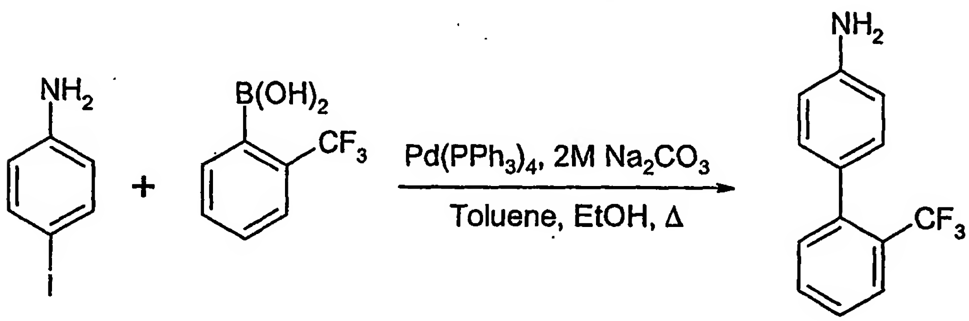


Following General Procedure 5, 1,2,3,4-tetrahydro-7-[2-(trifluoromethyl)phenyl]-isoquinoline (0.0509 g, 0.184 mmol) and 2-(phenyl)oxirane (0.021 mL, 0.0877 mmol) were combined and heated at 90 °C for 14 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.0138 g, 15%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.80 (d, *J*=8.0 Hz, 1H), 7.67 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.53-7.47 (m, 2H), 7.44-7.32 (m, 5H), 7.29 (d, *J*=8.4 Hz, 1H), 7.27-7.14 (br m, 1H), 5.25 (dd, *J*=3.6 Hz, *J*=10.4 Hz, 1H), 4.88-4.43 (br m, 2H), 4.13-3.90 (br m, 1H), 3.62-3.14 (br m, 5H). MS (ESI) $(M+H)^+ = 398$. Anal. Calcd for $C_{24}H_{22}F_3NO$+1.1 TFA: C, 60.19; H, 4.45; N, 2.68. Found: C, 60.16; H, 4.38; N, 2.61.

Example 9: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]amino]- 2-propanol

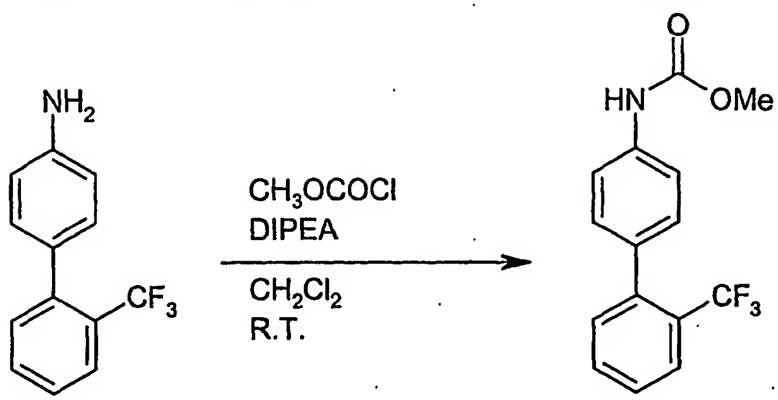


Compound 9a: 2'-(Trifluoromethyl)- [1,1'-biphenyl]-4-amine



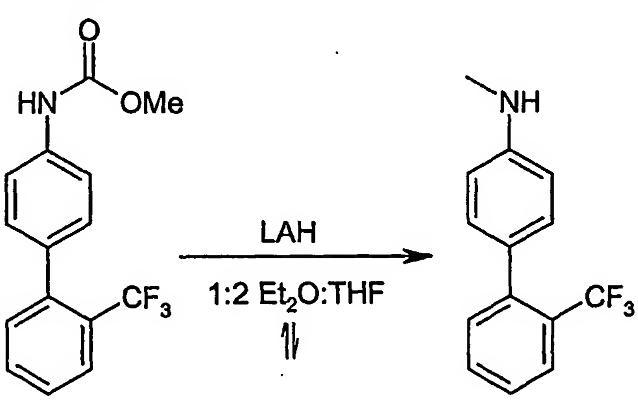
Following General Procedure 1, 4-iodoaniline(1.00 g, 4.57 mmol), 2-(trifluoromethyl)phenylboronic acid (1.302 g, 6.86 mmol), $Pd(PPh_3)_4$ (0.265 g, 0.23 mmol), and 2 M Na_2CO_3 (16 mL, 32 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound (0.476 g, 44%). ^{1}H-NMR ($CDCl_3$): δ 7.71 (dd, *J*=0.4 Hz, *J*=7.8 Hz, 1H), 7.52 (t, *J*=7.4 Hz, 1H), 7.41 (t, *J*=7.8 Hz, 1H), 7.32 (dd, *J*=0.4 Hz, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.2 Hz, 1H), 6.73-6.69 (m, 2H), 3.73 (br s, 2H). MS (ESI) $(M+H)^+$ = 238.

Compound 9b: Methyl [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]carbamate



To a solution of 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-amine (0.476 g, 2.01 mmol) and DIPEA (0.45 mL, 2.61 mmol) in CH_2Cl_2 (4.5 mL) maintained at 0 °C was added methylchloroformate (0.17 mL, 2.21 mmol). The reaction was allowed to slowly warm to room temperature, stirred overnight, diluted with CH_2Cl_2 (15 mL), and washed with 1 N HCl (2 x 20 mL) and brine (1 x 20 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (0.563 g, 95%) as a beige solid. ^{1}H-NMR ($CDCl_3$): δ 7.74 (dd, *J*=0.6 Hz, *J*=7.8 Hz, 1H), 7.50 (t, *J*=7.8 Hz, 1H), 7.47-7.42 (overlapping d and t, *J*=8.0 Hz for d and *J*=8.4 Hz for t, 3H), 7.32 (d, *J*=8.0 Hz, 1H), 7.28 (d, *J*=8.4 Hz, 2H), 6.69 (br s, 1H), 3.80 (s, 3H). MS (ESI) $(M+H)^+$ = 296.

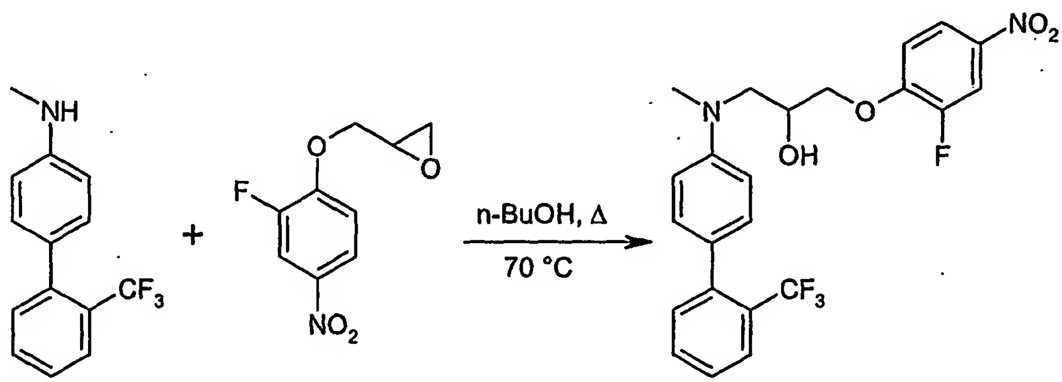
Compound 9c: N-Methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine



To a solution of methyl [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]carbamate (0.554 g, 1.88 mmol) in 1:2 dry Et_2O:THF (30 mL) was added LAH in Et_2O (2.82 mL, 2.82 mmol) dropwise. The reaction was refluxed for 4 hrs, cooled down to room

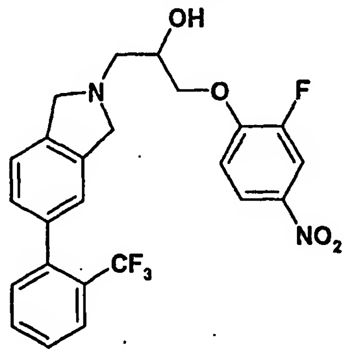
temperature, diluted with Et_2O (40 mL), and quenched with $Na_2SO_4{\cdot}5H_2O$ (2 g). The reaction mixture was stirred until the solution turned clear, filtered, and concentrated *in vacuo* to provide the title compound (0.409 g, 87%) as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ 7.71 (d, *J*=8.2 Hz, 1H), 7.52 (t, *J*=7.6 Hz, 1H), 7.40 (t, *J*=7.6 Hz, 1H), 7.33 (d, *J*=7.4 Hz, 1H), 7.17 (d, *J*=8.2 Hz, 2H), 6.64 (d, *J*=8.8 Hz, 2H), 2.88 (s, 3H). MS (ESI) $(M+H)^+$ = 252.

Compound 9d: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]amino]- 2-propanol

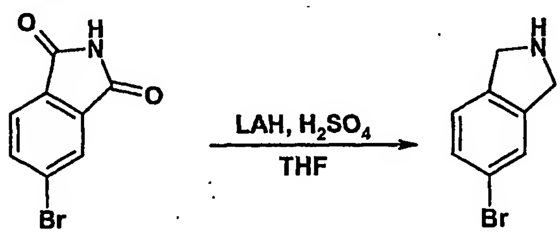


Following General Procedure 5, N-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (0.100 g, 0.40 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.085 g, 0.33 mmol) were combined and heated at 70 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 40-80% CH_3CN in H_2O) to provide the title compound (0.077 g, 42%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a yellow solid. ^{1}H-NMR (CD_3OD): δ 8.07-8.02 (m, 2H), 7.71 (d, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.4 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.29-7.49 (m, 4H), 7.03 (br d, *J*=7.6 Hz, 2H), 4.24-4.14 (m, 3H), 3.79 (dd, *J*=5.0 Hz, *J*=14.2 Hz, 1H), 3.57 (dd, *J*=7.2 Hz, *J*=14.4 Hz, 1H), 3.14 (s, 3H). MS (ESI) $(M+H)^+$ = 465. Anal. Calcd for $C_{23}H_{20}F_4N_2O_4$ + 0.2 H_2O + 0.3 TFA: C, 56.44; H, 4.15; N, 5.58. Found: C, 56.41; H, 4.05; N, 5.53.

Example 10: α-[(2-Fluoro-4-nitrophenoxy)methyl]-1,3-dihydro-5-[2-(trifluoromethyl)phenyl]-2*H*-isoindole-2-ethanol

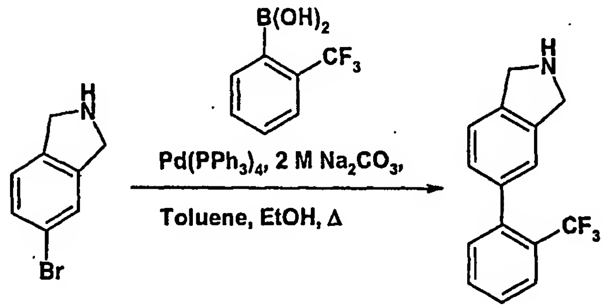


Compound 10a: 5-Bromo-2,3-dihydro-1*H*-isoindole



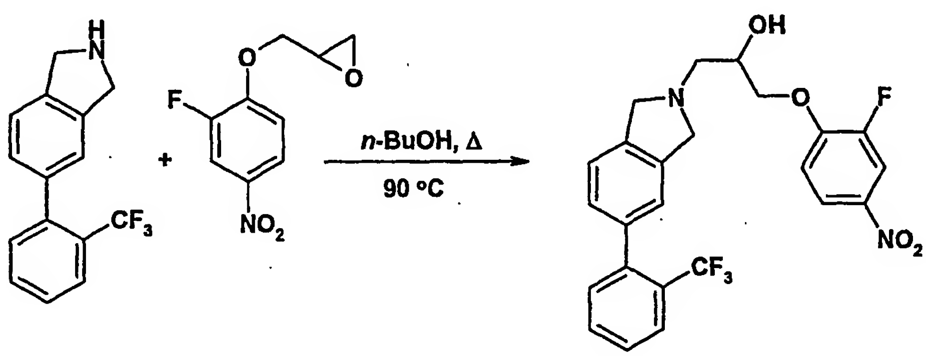
A solution of $LiAlH_4$ (8.8 mL of 1 M solution in Et_2O, 8.8 mmol) in dry THF (13 mL) was cooled to 0 °C. Concentrated H_2SO_4 (0.42 g, 4.3 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 min. 5-Bromo-1*H*-isoindole-1,3(2*H*)-dione (0.409 g, 1.81 mmol) was added in portions over 15 minutes, and the reaction was allowed to warm to room temperature when the addition was complete. The reaction was stirred at room temperature for 2.5h, and then cooled back to 0 °C and quenched by the addition of MeOH (2 mL). Et_2O was added (50 mL), followed by $Na_2SO_4 \cdot 10H_2O$. The mixture was stirred vigorously until the organic layer was clear. The mixture was then filtered and concentrated *in vacuo*. Purification by column chromatography (4:1 CH_2Cl_2:MeOH + 0.1% conc. NH_3) provided the title compound (0.128 g, 36%). ^{1}H-NMR ($CDCl_3$): δ 7.38 (s 1H), 7.33 (d, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 4.21 (s, 2H), 4.17 (s, 2H), 2.09 (s, 1H). MS (ESI) $(M+H)^+$ = 198/200.

Compound 10b: 2,3-Dihydro-5-[2-(trifluoromethyl)phenyl]-1*H*-isoindole



Following General Procedure 1, 5-bromo-2,3-dihydro-1*H*-isoindole (0.128 g, 0.647 mmol) was reacted with [2-(trifluoromethyl)phenyl]boronic acid (0.184 g, 0.971 mmol) to provide the title compound (0.124 g, 73%) following purification by column chromatography (85:15 CH_2Cl_2:MeOH + 0.1% conc. NH_3). ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, *J*=8.0 Hz, 1H), 7.55 (t, *J*=8.4 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.32 (d, *J*=7.2 Hz, 1H), 7.28 (d, *J*=7.6 Hz, 1H), 7.21 (s, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 4.30 (s, 2H), 4.29 (s, 2H), 2.34 (br s, 1H). MS (ESI) $(M+H)^+$ = 264.

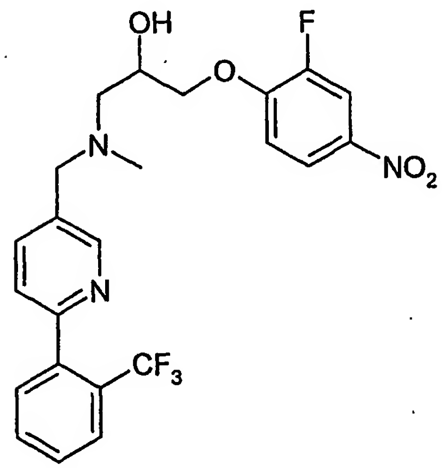
Compound 10c: α-[(2-Fluoro-4-nitrophenoxy)methyl]-1,3-dihydro-5-[2-(trifluoromethyl)phenyl]-2*H*-isoindole-2-ethanol



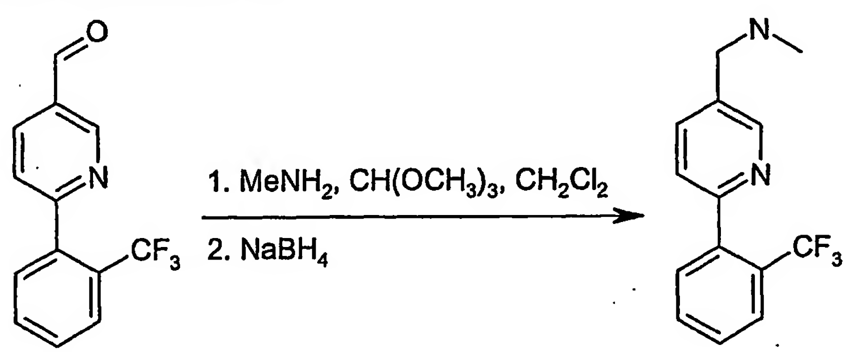
Following General Procedure 5, 2,3-dihydro-5-[2-(trifluoromethyl)phenyl]-1*H*-isoindole (0.0585 g, 0.222 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]-oxirane (0.0474 g, 0.222 mmol) were combined and heated at 90 °C for 14 h. The crude product was purified by reverse phase HPLC (gradient 20-65% CH_3CN in H_2O) to provide the title compound (0.0374 g, 29%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.13 (ddd, *J*=1.6 Hz, *J*=2.8 Hz, *J*=9.2 Hz, 1H),

8.09 (dd, J=2.8 Hz, J=11.2 Hz, 1H), 7.81 (d, J=7.6 Hz, 1H), 7.68 (t, J=7.2 Hz, 1H), 7.59 (t, J=7.6 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 7.42-7.33 (m, 4H), 5.08-4.74 (br s, 4H), 4.52 (sextet, J=4.8 Hz, 1H), 4.30 (d, J=4.8 Hz, 2H), 3.79-3.68 (m, 2H). MS (ESI) $(M+H)^+$ = 477. Anal. Calcd for $C_{24}H_{20}F_4N_2O_4$+0.6 TFA+2.5 H_2O: C, 51.31; H, 4.37; N, 4.75. Found: C, 51.29; H, 4.38; N, 4.54.

Example 11: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]- 2-propanol



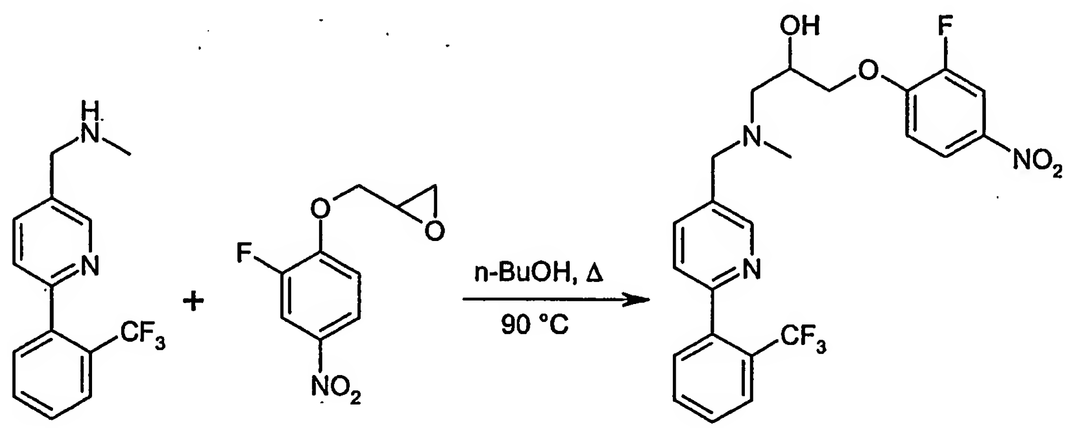
Compound 11a: *N*-Methyl-6-[2-(trifluoromethyl)phenyl]-3-pyridinemethanamine



6-[2-(Trifluoromethyl)phenyl]-3-pyridinecarboxaldehyde (0.360 g, 1.43 mmol) was treated according to General Procedure 3 to provide the title compound (0.312 g, 91%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 8.62 (d, J=1.6 Hz, 1H), 7.76 (d, J=7.6 Hz, 1H), 7.73 (d,

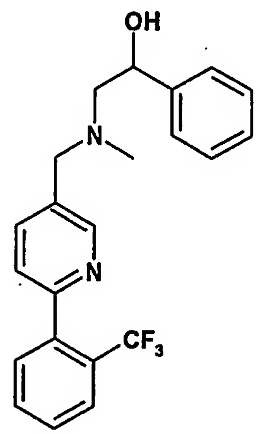
J=2.0 Hz, 1H), 7.61 (t, *J*=7.6 Hz, 1H), 7.54-7.48 (m, 2H), 7.40 (d, *J*=8.0 Hz, 1H), 3.84 (s, 2H), 2.50 (s, 3H). MS (ESI) $(M+H)^+ = 267$.

Compound 11b: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]- 2-propanol

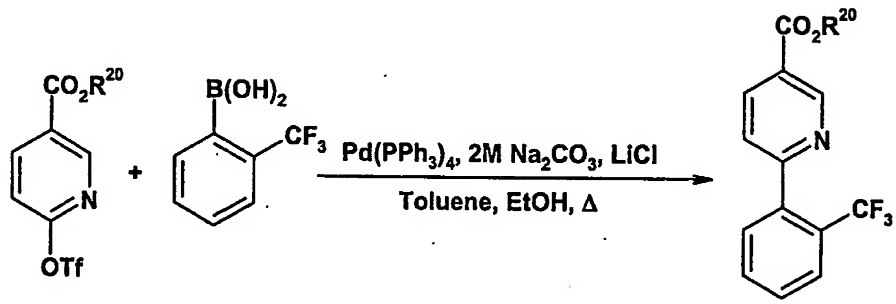


Following General Procedure 5, *N*-methyl-6-[2-(trifluoromethyl)phenyl]-3-pyridinemethanamine (0.100 g, 0.38 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.094 g, 0.38 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-50% CH_3CN in H_2O) to provide the title compound (0.071 g, 31%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. ^{1}H-NMR (CD_3OD): δ 8.78 (d, *J*=1.6 Hz, 1H), 8.13-8.03 (m, 3H), 7.84 (d, *J*=7.6 Hz, 1H), 7.74 (t, *J*=7.2 Hz, 1H), 7.67 (d, *J*=8.0 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=7.6 Hz, 1H), 7.30 (t, *J*=8.6 Hz, 1H), 4.66 (br s, 1H), 4.53 (br s, 2H), 4.23 (d, *J*=4.8 Hz, 2H), 3.43 (t, *J*=10.0 Hz, 2H), 2.99 (s, 3H). MS (ESI) $(M+H)^+ = 480$. Anal. Calcd for $C_{23}H_{21}F_4N_3O_4$ + 0.8 H_2O + 1.2 TFA: C, 48.37; H, 3.80; N, 6.66. Found: C, 48.37; H, 3.70; N, 6.79.

Example 12: α-[[Methyl-{[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]methyl]-benzenemethanol



Compound 12a: Methyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate and Ethyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate

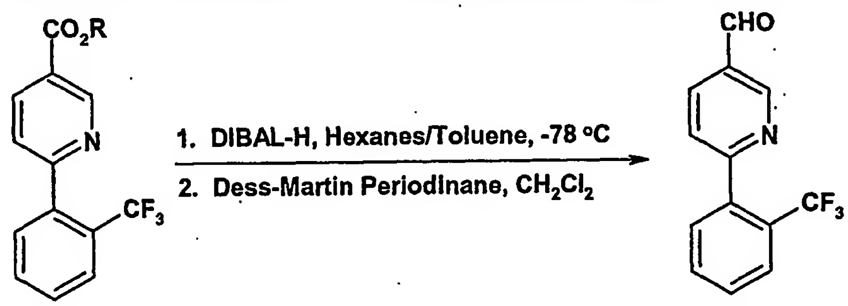


R^{20} = Methyl, or Ethyl

A solution of [2-(trifluoromethyl)phenyl]boronic acid (2.27 g, 12.0 mmol) in ethanol (30 mL) was added to a mixture of methyl 6-[[(trifluoromethyl)sulfonyl]oxy]-3-pyridinecarboxylate (2.27 g, 7.96 mmol), LiCl (1.01 g, 23.9 mmol), $Pd(PPh_3)_4$ (0.46 g, 0.40 mmol), toluene (120 mL), and 2 M Na_2CO_3 (12 mL). The resulting mixture was heated at reflux for 18 h. The reaction was then concentrated *in vacuo*, and the residue was diluted with water (60 mL). The aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic phases were then washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide the title compound as a 1:1.4 mixture of the methyl and ethyl esters (1.59 g, 69%). Methyl

ester: ^{1}H-NMR ($CDCl_3$): δ 9.30 (dd, J=0.8 Hz, J=2.0 Hz, 1H), 8.37 (dd, J=2.4 Hz, J=7.2 Hz, 1H), 7.80 (dd, J=0.8 Hz, J=8.0 Hz, 1H), 7.65 (t, J=7.6 Hz, 1H), 7.67-7.50 (m, 3H), 4.00 (s, 3H). MS (ESI) $(M+H)^+$ = 282. Ethyl ester: ^{1}H-NMR ($CDCl_3$): δ 9.29 (dd, J=0.8 Hz, J=2.4 Hz, 1H), 8.37 (dd, J=2.4 Hz, J=8.4 Hz, 1H), 7.79 (dd, J=0.8 Hz, J=8.4 Hz, 1H), 7.65 (t, J=7.6 Hz, 1H), 7.60-7.50 (m, 3H), 4.45 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H). MS (ESI) $(M+H)^+$ = 296.

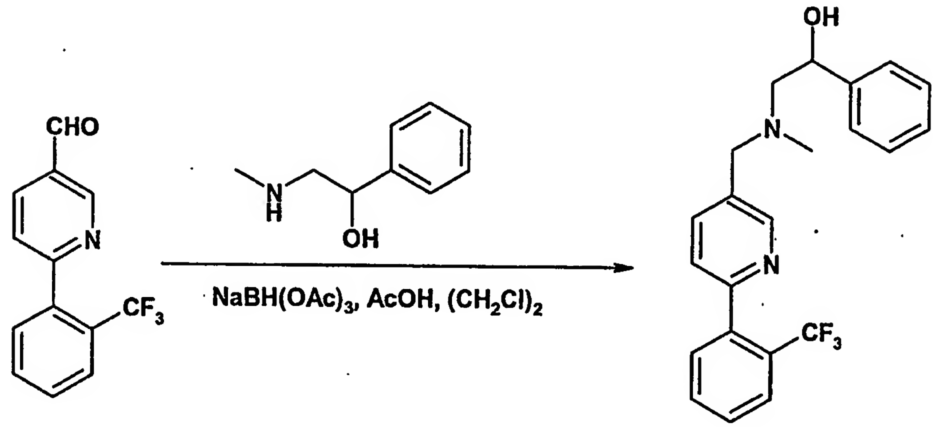
Compound 12b: 6-[2-(Trifluoromethyl)phenyl]-3-pyridinecarboxaldehyde



DIBAL-H (12.1 mL of a 1 M solution in hexanes, 12.1 mmol) was added dropwise to a solution of a mixture of methyl and ethyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate (1.59 g of a 1:1.4 mixture, 5.50 mmol) in dry toluene (45 mL) maintained at –78 °C. After the addition was complete, the reaction was stirred at –78 °C for 30 min, and then 12 mL of 1 N HCl was added cautiously and the mixture was allowed to warm to room temperature. Additional water (30 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and Dess-Martin periodinane (2.36 g, 5.57 mmol) was added in portions. After the addition was complete, the reaction was stirred at room temperature for 2 h. The reaction was then quenched with 1:1 saturated $NaHCO_3$:saturated $Na_2S_2O_3$ (40 mL) and stirred for 15 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (3:2 Hexanes:EtOAc) to provide the title compound (1.23 g, 89% for the two steps) as a slightly yellow oil which solidified upon storage in the freezer. ^{1}H-NMR ($CDCl_3$): δ 10.19 (s, 1H), 9.16

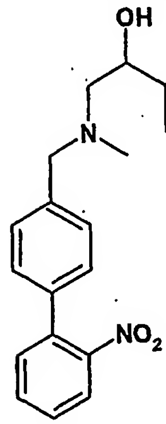
(dd, J=0.8 Hz, J=2.0 Hz, 1H), 8.25 (dd, J=2.4 Hz, J=8.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.70-7.56 (m, 3H), 7.52 (d, J=7.6 Hz, 1H). MS (ESI) $(M+H)^+$ = 252.

Compound 12c: α-[[Methyl-[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]methyl]-benzenemethanol

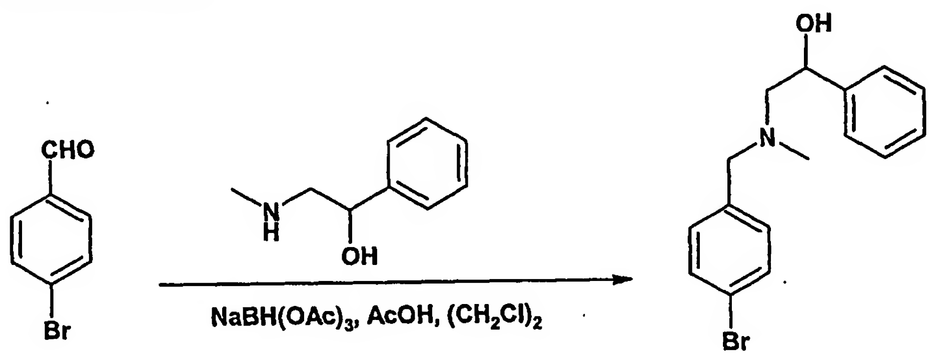


Following General Procedure 4, 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxaldehyde (0.166 g, 0.66 mmol), α-[(methylamino)methyl]benzenemethanol (0.100 g, 0.66 mmol), and $NaBH(OAc)_3$ (0.280 g, 1.32 mmol) were combined. The crude product was purified by reverse phase HPLC (gradient 20-40% CH_3CN in H_2O) to provide the title compound (0.279 g, 84%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. ^{1}H-NMR (CD_3OD): δ 8.81 (s, 1H), 8.14 (d, J=8.0 Hz, 1H), 7.86 (d, J=8.0 Hz, 1H), 7.57 (t, J=7.2 Hz, 1H), 7.72-7.64 (m, 2H), 7.55 (d, J=7.2 Hz, 1H), 7.48-7.31 (m, 5H), 5.17 (br m, 1H), 4.54 (br s, 2H), 3.33 (br s, 2H), 3.03 (br s, 3H). MS (ESI) $(M+H)^+$ = 387. Anal. Calcd for $C_{22}H_{21}F_3N_2O$+1.2 TFA+1.1 H_2O: C, 53.97; H, 4.53; N, 5.16. Found: C, 54.00; H, 4.43; N, 5.52.

Example 13: α-[[Methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol

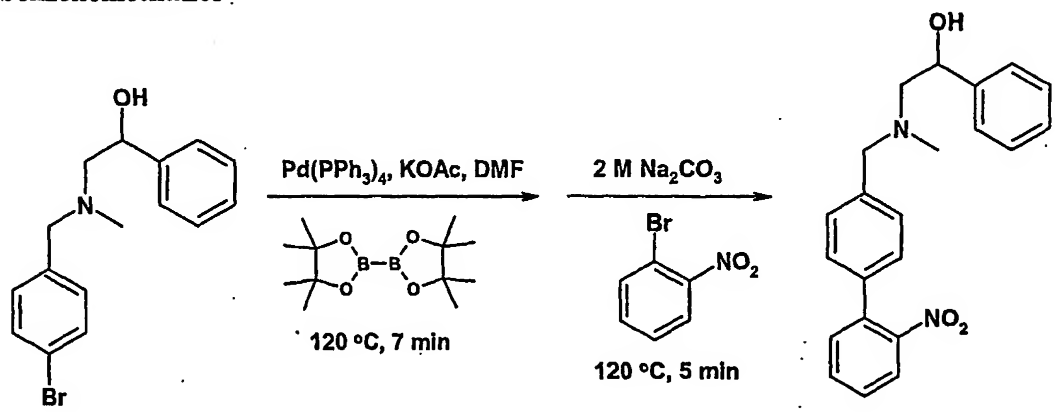


Compound 13a: α-[[[(4-Bromophenyl)methyl]methylamino]methyl] benzenemethanol



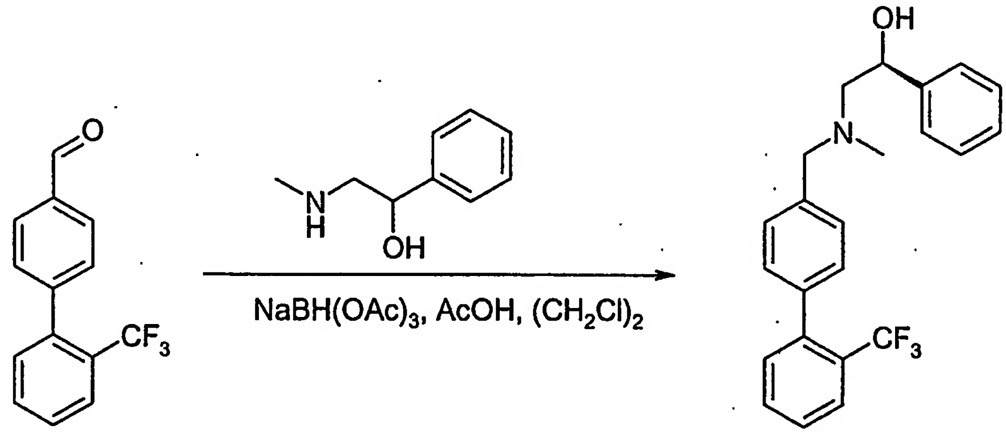
Following General Procedure 4, 4-bromobenzaldehyde (1.22 g, 6.59 mmol), α-[(methylamino)methyl]benzenemethanol (0.500 g, 3.31 mmol), and $NaBH(OAc)_3$ (1.40 g, 6.61 mmol) were combined. The crude product was purified by flash chromatography (Gradient of 100% CH_2Cl_2 to 9:1 CH_2Cl_2:MeOH + 0.1% conc. NH_3) to provide the title compound (0.942 g, 89%). ^{1}H-NMR (CD_3OD): δ 7.48-7.44 (m, 2H), 7.36-7.32 (m, 4H), 7.32-7.24 (m, 1H), 7.21-7.17 (m, 2H), 4.75 (dd, J=3.6 Hz, J=10.4 Hz, 1H), 3.69 (d, J=13.2 Hz, 1H), 3.48 (d, J=13.2 Hz, 1H), 2.59 (half of d of AB_q, J=10.4 Hz, J=12.4 Hz, 1H), 2.52 (half of d of AB_q, J=3.2 Hz, J=12.4 Hz, 1H), 2.31 (s, 3H). MS (ESI) $(M+H)^+$ = 320/322.

Compound 13b: α-[[Methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol



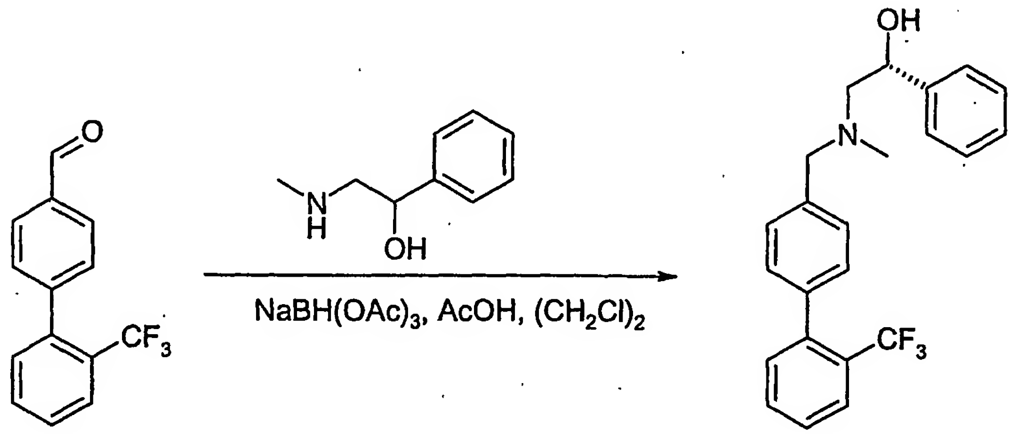
Following General Procedure 2, α-[[[(4-bromophenyl)methyl]methylamino]-methyl]benzenemethanol (0.0530 g, 0.165 mmol) and bis(pinacolato)diboron (0.0462 g, 0.182 mmol) were combined. The resulting boronate ester was used for the reaction with 1-bromo-2-nitrobenzene (0.0669 g, 0.331 mmol) as the second aryl halide. The crude product was purified by reverse phase HPLC (gradient 25-45% CH_3CN in H_2O) to provide the title compound (0.0113 g, 14%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.96 (d, *J*=8.0 Hz, 1H), 7.75 (t, *J*=7.2 Hz, 1H), 7.70-7.57 (br m, 3H), 7.57-7.29 (br m, 8H), 5.11 (dd, *J*=3.6 Hz, *J*=10.8 Hz, 1H), 4.75 (br d, *J*=12.8 Hz, 0.5H), 4.54-4.44 (br m, 1H), 4.32 (br d, *J*=12.0 Hz, 0.5H), 3.48-3.15 (br m, 2H), 3.07 (s, 1.5H), 2.91 (s, 1.5H). MS (ESI) $(M+H)^+$ = 363. Anal. Calcd for $C_{22}H_{22}N_2O_3$+1.1 TFA+1.1 H_2O: C, 57.25; H, 5.02; N, 5.52. Found: C, 57.26; H, 4.97; N, 5.46.

Example 14: (α^1S)-α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol



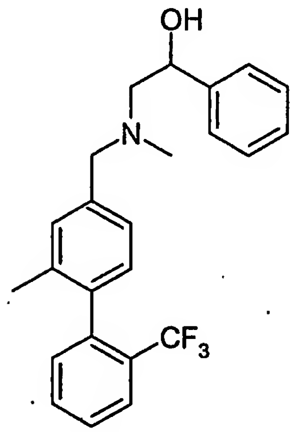
Following General Procedure 4, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.375 g, 1.50 mmol), α-[(methylamino)methyl]benzenemethanol (0.453 g, 3.00 mmol), and $NaBH(OAc)_3$ (0.636 g, 3.00 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound as a racemic mixture. Subsequent chromatography using CHIRALCEL®OD (990:10:1 EtOH:Hex:Et_2NH) gave the title compound. The HCl salt of the title compound (0.0102 g, 3%) was prepared using 1M HCl in Et_2O. This material was lyophilized to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $[\alpha]_D^{24} = +44.2°$ (c=1.02, MeOH). ^{1}H-NMR (CD_3OD): δ 7.80 (d, *J*=7.6 Hz, 1H), 7.69-7.56 (overlapping t at 7.67 and m, *J*=7.4 Hz, 4H), 7.46-7.32 (overlapping d at 7.45 and br m, *J*=8.0 Hz, 8H), 5.11 (dd, *J*=6.8 Hz, *J*=7.2 Hz, 1H), 4.85-4.35 (br m, 2H), 3.26 (br s, 2H), 3.00 (br s, 3H). MS (ESI) $(M+H)^+ = 386$. Anal. Calcd for $C_{23}H_{22}F_3NO + 0.1\ H_2O + 1.2\ HCl$: C, 64.10; H, 5.47; N, 3.25. Found: C, 64.15; H, 5.33; N, 3.80.

Example 15: (α^1R)-α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol

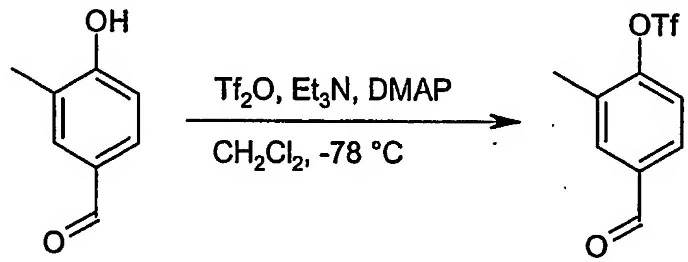


Following General Procedure 4, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.375 g, 1.50 mmol), α-[(methylamino)methyl]benzenemethanol (0.453 g, 3.00 mmol), and $NaBH(OAc)_3$ (0.636 g, 3.00 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound as a racemic mixture. Subsequent chromatography using CHIRALCEL®OD (990:10:1 EtOH:Hex:Et_2NH) gave the title compound. The HCl salt of the title compound (0.0056 g, 2%) was prepared using 1M HCl in Et_2O. This material was lyophilized to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $[\alpha]_D^{28}$ = -49.5° (c=0.56, MeOH). ^{1}H-NMR (CD_3OD): δ 7.79 (d, J=8.0 Hz, 1H), 7.68-7.55 (overlapping t at 7.66 and m, J=7.6 Hz, 4H), 7.45-7.30 (overlapping d at 7.44 and br m, J=7.6 Hz, 8H), 5.10 (dd, J=6.4 Hz, J=7.6 Hz, 1H), 4.84-4.33 (br m, 2H), 3.25 (br s, 2H), 2.98 (br s, 3H). MS (ESI) $(M+H)^+$ = 386. Anal. Calcd for $C_{23}H_{22}F_3NO$ + 1.5 HCl: C, 62.77; H, 5.38; N, 3.18. Found: C, 62.89; H, 5.31; N, 3.40.

Example 16: α-[[Methyl[[2-methyl-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

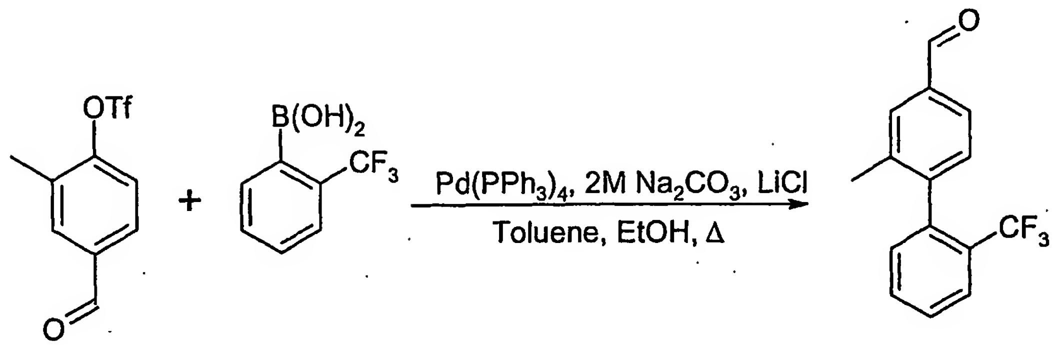


Compound 16a: 4-Formyl-2-methylphenyl trifluoromethanesulfonate



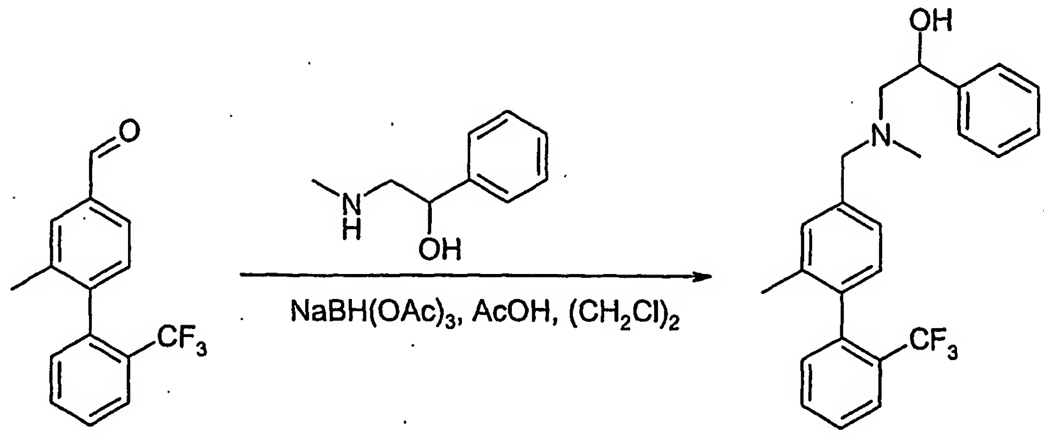
Following General Procedure 7, 4-hydroxy-3-methylbenzaldehyde (0.500 g, 3.67 mmol), DMAP (0.045 g, 0.37 mmol), NEt_3 (1.126 mL, 8.08 mmol), and triflic anhydride (1.139 g, 4.04 mmol) were combined. Silica gel column chromatography (8:2 Hexanes:EtOAc) provided the title compound (0.896 g, 91%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 10.01 (s, 1H), 7.86 (s, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.44 (d, J=7.6 Hz, 1H), 2.48 (s, 3H).

Compound 16b: 2-Methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde



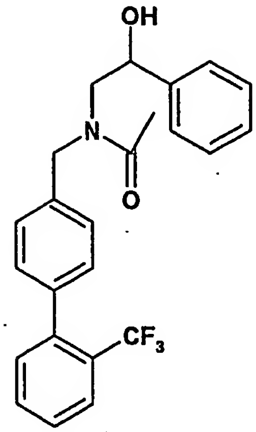
A solution of [2-(trifluoromethyl)phenyl]boronic acid (2.79 g, 14.66 mmol) in ethanol (35 mL) was added to a mixture of 4-formyl-2-methylphenyl trifluoromethanesulfonate (2.62 g, 9.78 mmol), LiCl (1.24 g, 29.33 mmol), $Pd(PPh_3)_4$ (0.57 g, 0.49 mmol), toluene (145 mL), and 2 M Na_2CO_3 (15 mL). The resulting mixture was heated at reflux for 24 h. The reaction was then concentrated *in vacuo*, and the residue was diluted with water (60 mL). The aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic phases were then washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (2.533 g, 95%). The crude material was of sufficient purity (>85%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 10.04 (s, 1H), 7.80-7.78 (overlapping s at 7.78 and d at 7.79, *J*=7.6 Hz, 2H), 7.73 (d, *J*=7.6 Hz, 1H), 7.61 (t, *J*=7.6 Hz, 1H), 7.53 (t, *J*=7.6 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 2.12 (s, 3H). MS (ESI) $(M+H)^+$ = 265.

Compound 16c: α-[[Methyl[[2-methyl-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

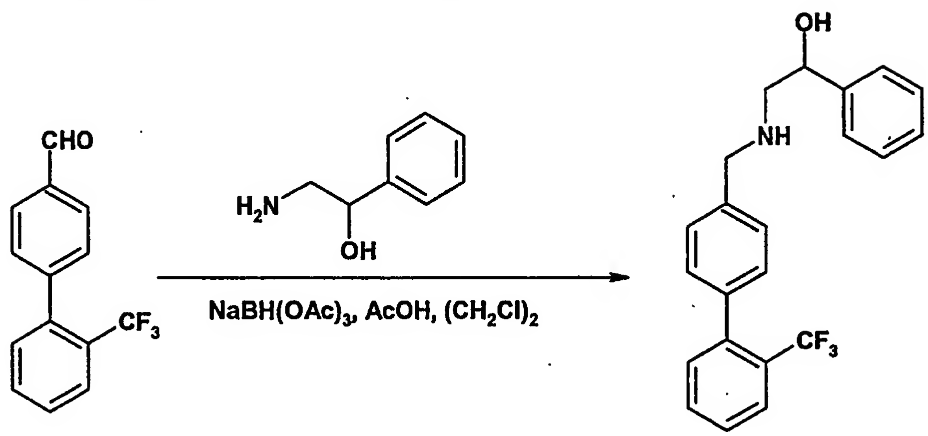


Following General Procedure 4, 2-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde (1.076 g, 3.55 mmol), α-[(methylamino)methyl]benzenemethanol (0.200 g, 1.32 mmol), and $NaBH(OAc)_3$ (0.562 g, 2.65 mmol) were combined. The crude product was purified by reverse phase HPLC (gradient 30-85% CH_3CN in H_2O) to provide the title compound (0.267 g, 40%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^1H-NMR (CD_3OD): δ 7.80 (d, J=7.6 Hz, 1H), 7.66 (t, J=7.6 Hz, 1H), 7.57 (t, J=7.6 Hz, 1H), 7.47-7.22 (overlapping d at 7.26 and br m, J=7.6 Hz, 9H), 5.09 (dd, J=3.2 Hz, J=10.8 Hz, 1H), 4.69 (br d, J=12.4 Hz, 0.5H), 4.47-4.37 (br m, 1H), 4.25 (br d, J=13.2 Hz, 0.5H), 3.41-3.13 (br m, 2H), 3.05 (br s, 1.5H), 2.89 (br s, 1.5H), 2.07-2.05 (overlapping s at 2.07 and s at 2.05, 3H). MS (ESI) $(M+H)^+$ = 400. Anal. Calcd for $C_{24}H_{24}F_3NO$ + 0.1 H_2O + 1.1 TFA: C, 59.75; H, 4.84; N, 2.66. Found: C, 59.73; H, 4.81; N, 2.75.

Example 17: *N*-(2-Hydroxy-2-phenylethyl)-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]acetamide

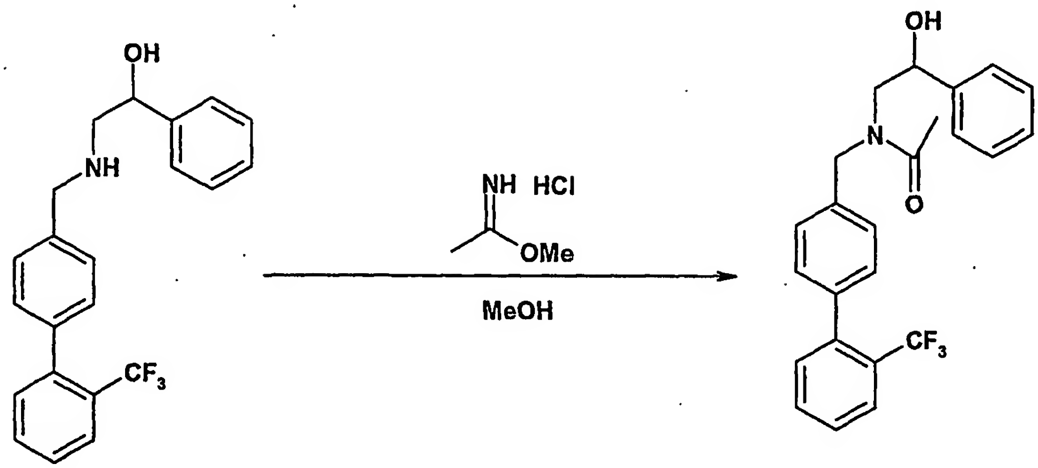


Compound 17a: α-[[[[2'-(Trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol



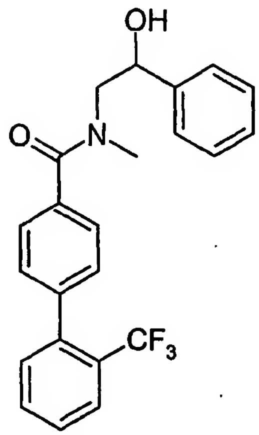
Following General Procedure 4, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.121 g, 0.484 mmol), α-(aminomethyl)benzenemethanol (0.0975 g, 0.711 mmol), and $NaBH(OAc)_3$ (0.179 g, 0.846 mmol) were combined. The crude product was purified by flash chromatography (9:1 CH_2Cl_2:MeOH) to provide the title compound (0.133 g, 74%). ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, *J*=8.0 Hz, 1H), 7.55 (t, *J*=7.2 Hz, 1H), 7.46 (t, *J*=8.0 Hz, 1H), 7.40-7.27 (m, 10H), 4.78 (dd, *J*=3.6 Hz, *J*=8.8 Hz, 1H), 3.89 (AB_q, *J*=13.2 Hz, 2H), 2.98 (dd, *J*=3.6 Hz, *J*=12.0 Hz, 1H), 2.81 (overlapping dd and br s, *J*=9.2 Hz, *J*=12.4 Hz for dd, 3H). MS (ESI) $(M+H)^+ = 372$.

Compound 17b: *N*-(2-Hydroxy-2-phenylethyl)-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]acetamide

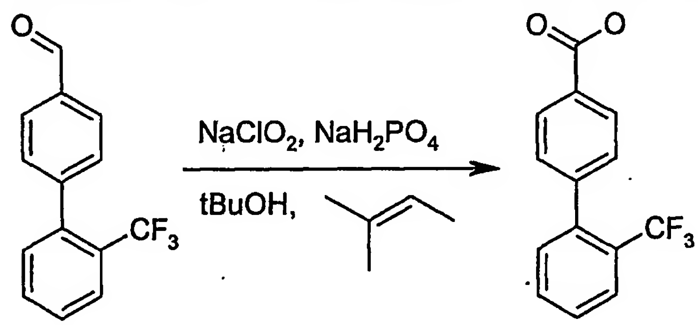


Methyl acetimidate hydrochloride (0.0847 g, 0.773 mmol) was added to a solution of α-[[[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol (0.0287 g, 0.0773 mmol) in dry MeOH (1 mL) maintained at 0 °C. The reaction was stirred for 6 d at room temperature, and then an additional portion of methyl acetimidate hydrochloride (0.0500 g, 0.456 mmol) was added. After stirring an additional 7 d, the reaction was concentrated *in vacuo*. The residue was dissolved in EtOAc (2 mL) and washed with a saturated solution of Na_2CO_3 (1 mL). The aqueous phase was back-extracted with additional EtOAc (3 x 1 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.0105 g, 33%). This material was lyophilized from H_2O/acetonitrile. Due to hindered rotation about the amide bond, rotamers were observed in the ^1H-NMR spectrum. ^1H-NMR (CD_3OD): δ 7.78-7.74 (m, 1H), 7.66-7.60 (m, 1H), 7.56-7.50 (m, 1H), 7.40-7.20 (m, 10H), 5.00 (dd, *J*=4.8 Hz, *J*=8.4 Hz, 0.4H), 4.93 (dd, *J*=4.8 Hz, *J*=8.0 Hz, 0.6H), 4.88 (d, *J*=14.8 Hz, 0.6H), 4.72 (d, *J*=17.2 Hz, 0.4H), 4.61-4.54 (m, 1H), 3.67-3.58 (m, 1H), 3.50 (dd, *J*=8.4 Hz, *J*=13.6 Hz, 0.4H), 3.39 (dd, *J*=4.8 Hz, *J*=15.2 Hz, 0.6H), 2.16 (s, 1.2H), 2.11 (s, 1.8H). MS (ESI) $(M+H)^+ = 414$. Anal. Calcd for $C_{24}H_{22}F_3NO_2$+0.3 TFA+0.6 H_2O: C, 64.45; H, 5.17; N, 3.06. Found: C, 64.55; H, 5.10; N, 3.50.

Example 18: *N*-(2-Hydroxy-2-phenylethyl)-*N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide

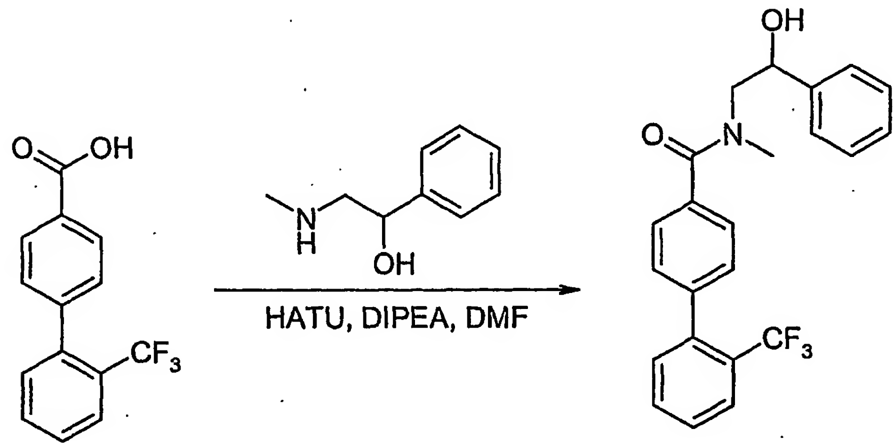


Compound 18a: 2'-(Trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid



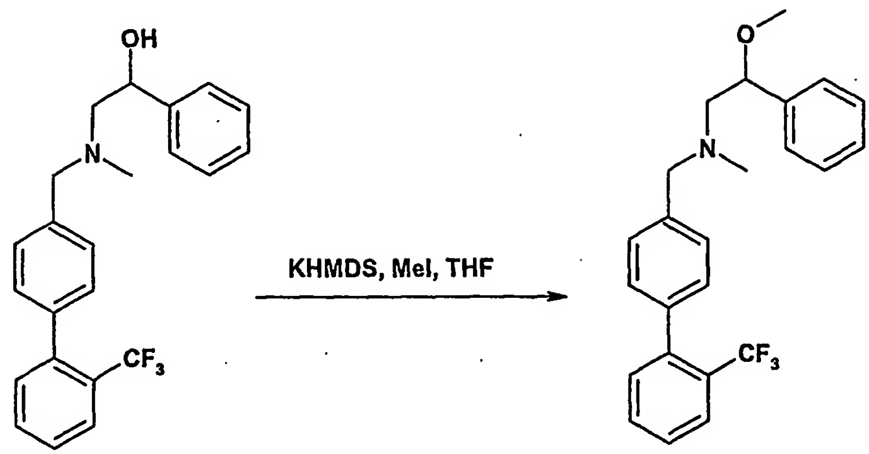
To a solution of 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.147 g, 0.59 mol) in t-BuOH (9 mL) and 2-methyl-2-butene (9 mL) was added a solution of $NaClO_2$ (0.496, 5.50 mmol) and NaH_2PO_4 (0.588 g, 4.9 mmol) in water (6 mL) in four portions over 0.5 h. The resulting reaction mixture was stirred for 5 h at room temperature, concentrated *in vacuo*, and the residue was diluted with water. The aqueous phase was extracted with CH_2Cl_2 (3 x). The product in the combined organic phases was then extracted into 1 N NaOH (3 x). The CH_2Cl_2 layer was discarded, the combined aqueous layers were acidified with 1 N HCl, and the product was back extracted with CH_2Cl_2 (3 x). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (0.125 g, 80%) as a white solid. The crude material was of sufficient purity (>90%) to be used in subsequent steps. ^{1}H-NMR (CD_3OD): δ 8.06 (d, *J*=8.0 Hz, 2H), 7.79 (d, *J*=7.6 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.42-7.36 (overlapping d at 7.41 and d at 7.37, *J*=8.0 Hz for both d, 3H).

Compound 18b: ***N*-(2-Hydroxy-2-phenylethyl)-*N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide**



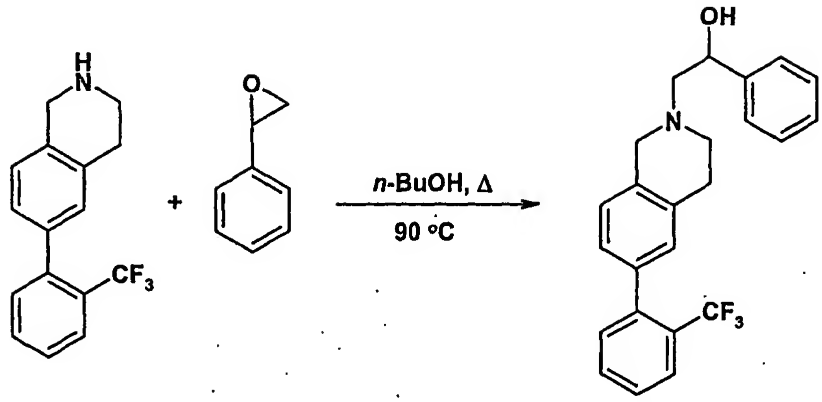
A solution of α-[(methylamino)methyl]benzenemethanol (0.013 g, 0.085 mmol) in DMF (0.5 mL) was added to a solution of 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid (0.025 g, 0.094 mmol), HATU (0.036 g, 0.094 mmol) and DIPEA (0.022 mL, 0.128 mmol) in DMF (0.5 mL). The reaction was carried out in a 48-well plate. The reaction was stirred overnight at room temperature, concentrated *in vacuo*, redissolved in EtOAc (1 mL), and washed with 1 N NaOH (3 x 1 mL) and water (2 x 1 mL). The organic phase was concentrated *in vacuo* to provide the title compound (0.027 g, 81%) with >90% purity. Due to hindered rotation about the amide bond, rotamers were observed in the ^{1}H-NMR spectrum. ^{1}H-NMR (CD_3OD): δ 7.77 (dd, *J*=2.0 Hz, *J*=7.6 Hz, 1H), 7.64 (t, *J*=7.4 Hz, 1H), 7.54 (t, *J*=7.6 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.40-7.22 (d at 7.30, *J*=8.0 Hz, d at 7.23, *J*=8.0 Hz, br m, 8H), 7.10-7.08 (m, 1H), 5.08 (t, *J*=6.6 Hz, 0.5H), 4.81 (t, *J*=6.4 Hz, 0.5H), 3.74-3.72 (m, 1H), 3.50 (t, *J*=6.6 Hz, 1H), 3.21 (s, 1.5H), 2.94 (s, 1.5H). MS (ESI) $(M+H)^+$ = 400.

Example 19: β-Methoxy-*N*-methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]-benzeneethanamine



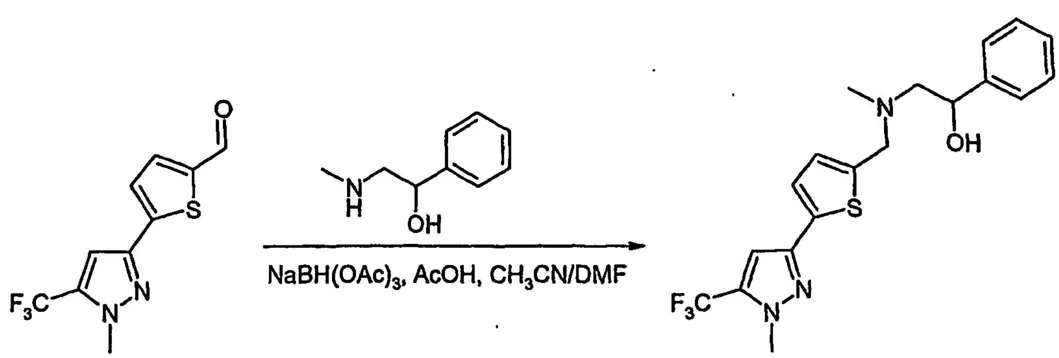
KHMDS (0.45 mL of 0.5M in toluene, 0.225 mmol) was added to a solution of α-[[methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzene-methanol (0.0286 g, 0.0742 mmol) in dry THF (3 mL). The mixture was stirred at room temperature for 20 min, and then neat iodomethane (4.6 μL, 0.074 mmol) was added. The reaction was stirred at room temperature for 19 h, and then quenched by the addition of H_2O (3 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 x 3 mL). The combined organic phases were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-70% CH_3CN in H_2O) to provide the title compound (0.0066 g, 17%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.82 (d, *J*=7.6 Hz, 1H), 7.72-7.56 (m, 4H), 7.54-7.30 (m, 8H), 4.78-4.65 (m, 1H), 4.62-4.42 (m, 1.5H), 4.36 (br d, *J*=12.4 Hz, 0.5H), 3.50-3.30 (m, 1.5H), 3.29 (s, 3H), 3.17 (br d, *J*=12.8 Hz, 0.5H), 3.06 (s, 1.5H), 2.94 (s, 1.5H). MS (ESI) $(M+H)^+ = 400$.

Example 20: 3,4-Dihydro-α-phenyl-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol



Following General Procedure 5, 1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]-isoquinoline (0.0247 g, 0.0891 mmol) and 2-(phenyl)oxirane (0.010 mL, 0.0877 mmol) were combined and heated at 90 °C for 16 h. The crude product was purified by reverse phase HPLC (gradient 25-45% CH_3CN in H_2O) to provide the title compound (0.0111 g, 24%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.79 (d, J=7.6 Hz, 1H), 7.67 (t, J=7.6 Hz, 1H), 7.57 (t, J=7.6 Hz, 1H), 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.24 (m, 5H), 5.27 (dd, J=3.2 Hz, J=10.0 Hz, 1H), 4.86-4.46 (br m, 2H), 4.12-3.90 (br m, 1H), 3.62-3.12 (br m, 5H). MS (ESI) $(M+H)^+$ = 398. Anal. Calcd for $C_{24}H_{22}F_3NO$+1.3 TFA+0.5 H_2O: C, 57.60; H, 4.42; N, 2.53. Found: C, 57.60; H, 4.35; N, 2.49.

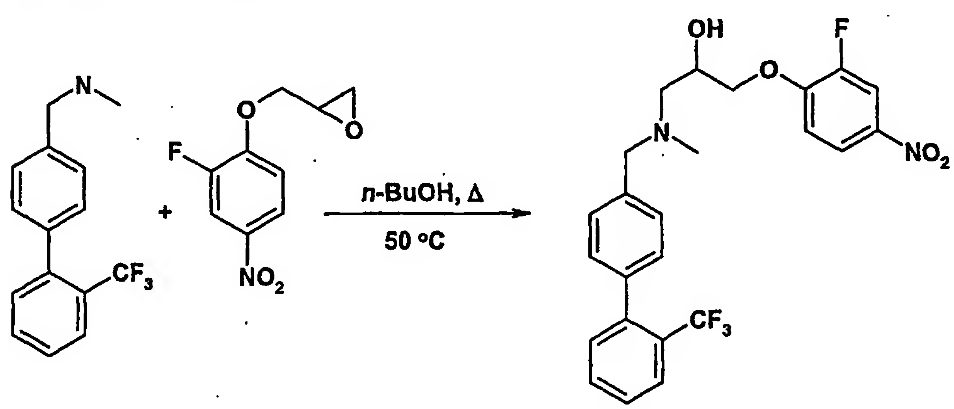
Example 21: α-[[Methyl[[5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl]methyl]amino]methyl]-benzenemethanol



A solution of 5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]- 2-thiophenecarboxaldehyde (0.260 g, 0.77 mmol), α-

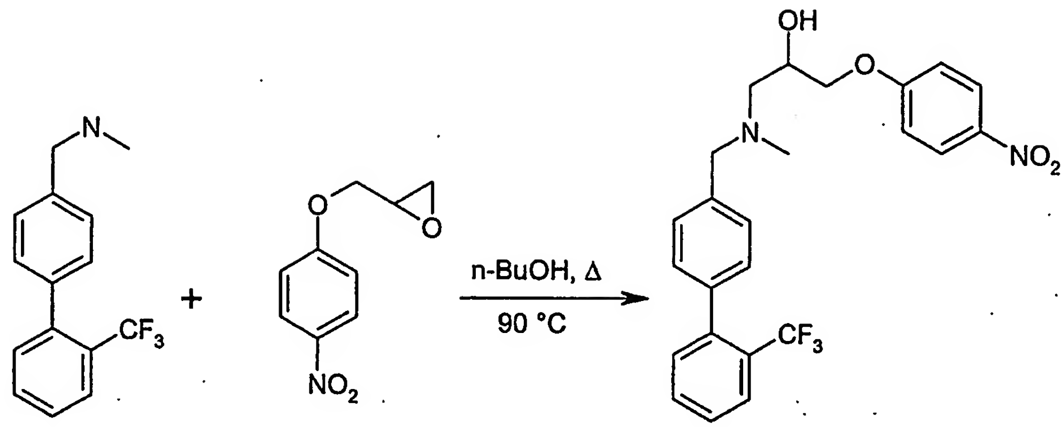
[(methylamino)methyl]benzenemethanol (0.151 g, 0.77 mmol), and acetic acid (0.080 mL) in CH_3CN (4 mL) was stirred for 3 days. A solution of $NaBH(OAc)_3$ (0.211 g, 3.87 mmol) in DMF (4 mL) was added and the reaction was stirred for 2 days, concentrated *in vacuo*, redissolved in CH_2Cl_2, and washed with 1 N NaOH. The layers were then filtered through a Hydromatrix® column and the product was eluted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 15-85% CH_3CN in H_2O) to provide the title compound (0.040 g, 10%) as its TFA salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.41-7.28 (br m, 7H), 6.81 (s, 1H), 5.10 (dd, *J*=6.0 Hz, *J*=7.6 Hz, 1H), 4.80-4.65 (br s at 4.75, s at 4.69, and s at 4.65, 2H), 4.01 (s, 3H), 3.33-3.27 (overlapping s at 3.33 and s at 3.30, 2H), 3.01 (br s, 3H). MS (ESI) $(M+H)^+ = 396$. Anal. Calcd for $C_{19}H_{20}F_3N_3OS$ + 0.2 H_2O + 1.0 TFA: C, 54.02; H, 4.25; N, 4.85. Found: C, 54.05; H, 4.09; N, 4.85.

Example 22: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol



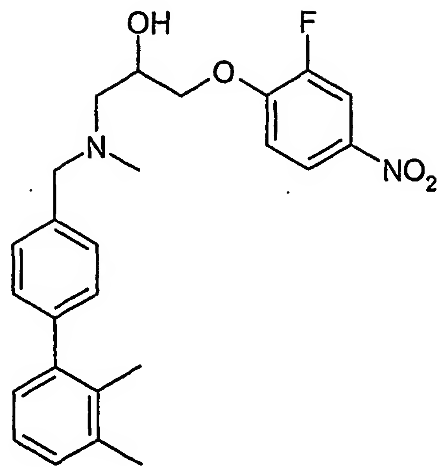
Following General Procedure 5, N-methyl-2'-(trifluoromethyl)- [1,1'-biphenyl]-4-methanamine (0.0800 g of 90% purity, 0.288 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.0613 g, 0.288 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.030 g, 18%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.08 (d, *J*=9.2 Hz, 1H), 8.04 (dd, *J*=2.0 Hz, *J*=11.2 Hz, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.60 (d, *J*=8.0 Hz, 2H), 7.57 (t, *J*=7.6 Hz, 1H), 7.44 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=7.6 Hz, 1H), 7.30 (t, *J*=8.4 Hz, 1H), 4.72-4.16 (br m at 4.51, br s at 4.21, and underlying br m, 5H), 3.62-3.24 (br s at 3.55, br t at 3.40, br s at 3.28, *J*=11.2 Hz for t, 2H), 2.97 (br s, 3H). MS (ESI) $(M+H)^+$ = 479. Anal. Calcd for $C_{24}H_{22}F_4N_2O_4$ + 0.1 H_2O + 1.2 TFA: C, 51.39; H, 3.82; N, 4.54. Found: C, 51.34; H, 3.73; N, 4.90.

Example 23: 1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-(4-nitrophenoxy)-2-propanol

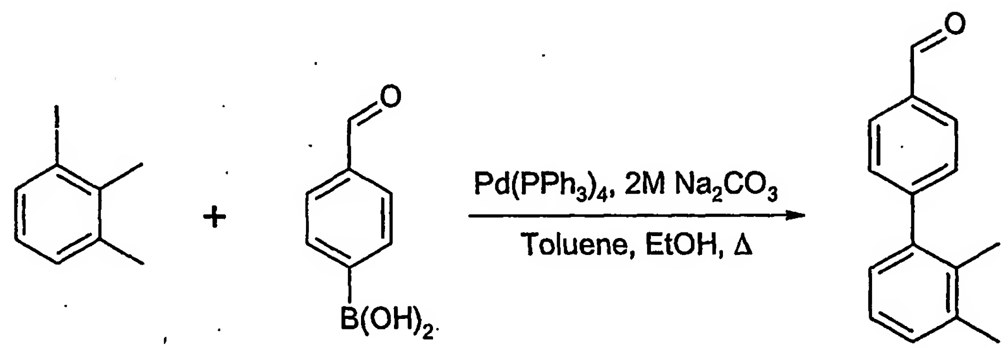


Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.072 g, 0.29 mmol) and 2-[(4-nitrophenoxy)methyl]-oxirane (0.057 g, 0.29 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.034 g, 20%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.20 (d, *J*=9.2 Hz, 2H), 7.79 (d, *J*=7.6 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.62-7.55 (overlapping d at 7.61 and t at 7.57, *J*=8.4 Hz for d and *J*=7.6 Hz for t, 3H), 7.44 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=7.6 Hz, 1H), 7.09 (br d, *J*=8.4 Hz, 2H), 4.64-4.31 (overlapping br s at 4.64, br s at 4.31, and br m, 3H), 4.13 (br s, 2H), 3.53-3.29 (br s at 3.53, br t at 3.38, and br s at 3.29, *J*=11.6 Hz for t, 2H), 2.97 (br s, 3H). MS (ESI) $(M+H)^+ = 461$. Anal. Calcd for $C_{24}H_{23}F_3N_2O_4$ + 0.2 H_2O + 1.0 TFA: C, 54.02; H, 4.25; N, 4.85. Found: C, 54.05; H, 4.09; N, 4.85.

Example 24: 1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol

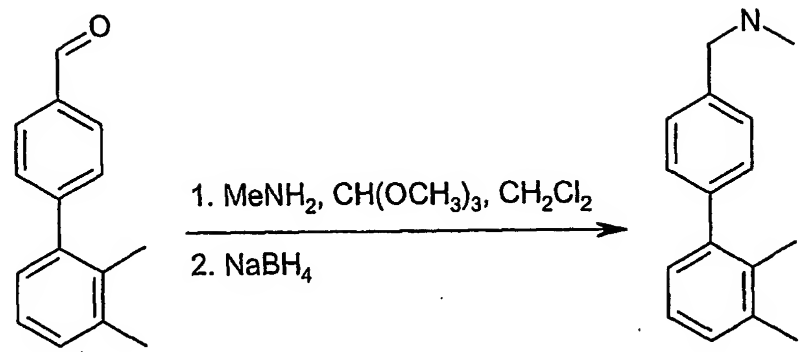


Compound 24a: 2',3'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde



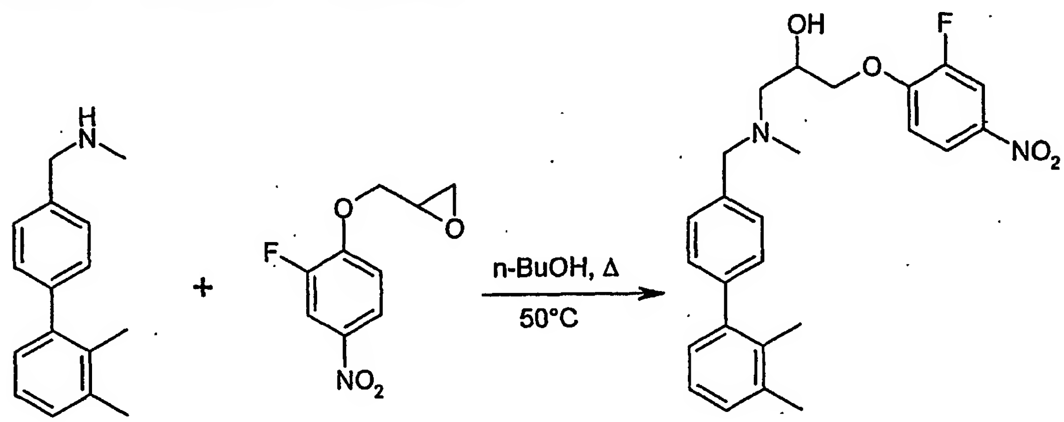
Following General Procedure 1, 1-iodo-2,3-dimethyl-benzene (2.06 g, 8.89 mmol), 4-formylphenylboronic acid (2.00 g, 13.34 mmol), $Pd(PPh_3)_4$ (0.51 g, 0.44 mmol), and 2 M Na_2CO_3 (31 mL, 62 mmol) were combined. Following the usual work-up provided the title compound (1.05 g, 56%). The crude material was of sufficient purity (>75%) to be used in the subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 10.07 (s, 1H), 7.93 (d, *J*=7.6 Hz, 2H), 7.47 (d, *J*=8.0 Hz, 2H), 7.22-7.15 (m, 2H), 7.07 (d, *J*=6.4 Hz, 1H), 2.36 (s, 3H), 2.15 (s, 3H).

Compound 24b: *N*,2',3'-Trimethyl-[1,1'-biphenyl]-4-methanamine



2',3'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde (0.351 g, 1.67 mmol) was treated according to General Procedure 3 to provide the title compound (0.120 g, 40%). The crude material was of sufficient purity (>80%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.34 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 7.15-7.06 (m, 3H), 3.79 (br s, 2H), 2.49 (br s, 3H), 2.33 (s, 3H), 2.15 (s, 3H). MS (ESI) $(M+H)^+ = 226$.

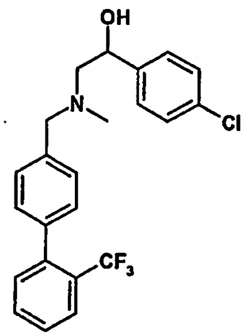
Compound 24c: 1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol



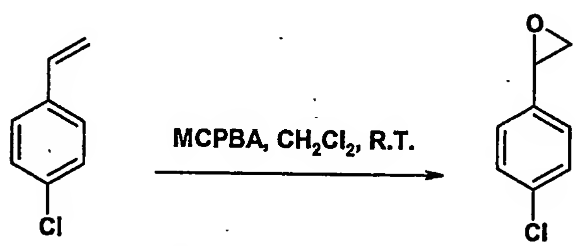
Following General Procedure 5, *N*,2',3'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.063 g, 0.30 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.64 g, 0.38 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.027 g, 16%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.09-8.02 (br m, 2H), 7.58 (d, *J*=8.0 Hz, 2H), 7.40 (d, *J*=8.0 Hz, 2H), 7.29 (br s, 1H), 7.15

(d, J=6.8 Hz, 1H), 7.10 (t, J=7.4 Hz, 1H), 6.98 (d, J=6.8 Hz, 1H), 4.62, (br s, 0.5H), 4.49 (br s, 2H), 4.27-4.26 (overlapping br s at 4.27 and br s at 4.26, 2.5H), 3.54-3.28 (br s at 3.54, br s at 3.39, and br s at 3.29, 2H), 3.00-2.95 (overlapping br s at 3.00 and br s at 2.95, 3H), 2.32 (s, 3H), 2.11 (s, 3H). MS (ESI) $(M+H)^+$ = 439. Anal. Calcd for $C_{25}H_{27}FN_2O_4$ + 0.1 H_2O + 1.6 TFA: C, 54.39; H, 4.66; N, 4.50. Found: C, 54.30; H, 4.48; N, 4.41.

Example 25: 4-Chloro-α-[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

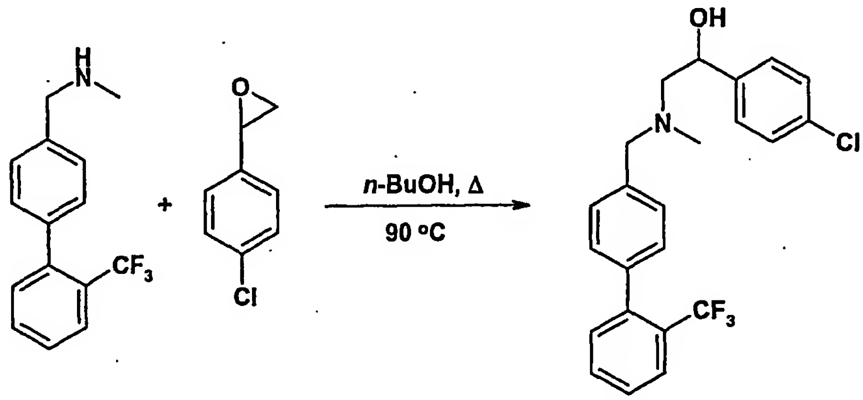


Compound 25a: 2-(4-Chlorophenyl)oxirane



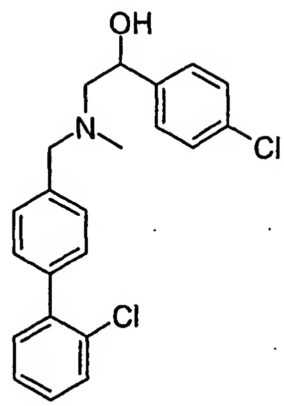
A solution of MCPBA (1.50 g of 60% purity, 5.22 mmol) in CH_2Cl_2 (10 mL) was added to a solution of 1-chloro-4-ethenylbenzene (0.554 g, 4.00 mmol) in CH_2Cl_2 (10 mL) maintained at 0 °C. The reaction was allowed to slowly warm to room temperature and stirred for 24 h. The mixture was filtered, and the filtrate was washed with saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (9:1 Hexanes:EtOAc) to provide the title compound (0.198 g, 32%). ^{1}H-NMR ($CDCl_3$): δ 7.31 (d, J=8.8 Hz, 2H), 7.20 (d, J=8.8 Hz, 2H), 3.83 (distorted t, J=3.6 Hz, 1H), 3.14 (dd, J=4.0 Hz, J=5.6 Hz, 1H), 2.75 (dd, J=2.4 Hz, J=5.6 Hz, 1H).

Compound 25b: 4-Chloro-α-[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

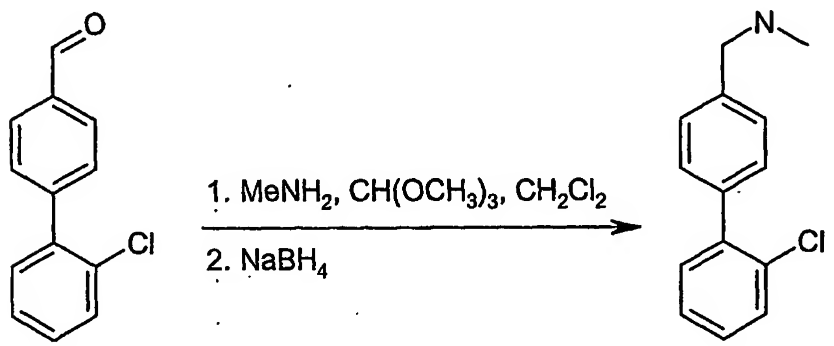


Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)- [1,1'-biphenyl]-4-methanamine (0.114 g of 90% purity, 0.387 mmol) and 2-(4-chlorophenyl)oxirane (0.060 g, 0.387 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH_3CN in H_2O) to provide the title compound (0.051 g, 24%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.78 (d, *J*=8.0 Hz, 1H), 7.65 (t, *J*=7.2 Hz, 1H), 7.62-7.52 (t and overlapping br m, *J*=7.6 Hz for t, 3H), 7.48-7.31 (m, 7H), 5.12-5.04 (m, 1H), 4.73 (br d, *J*=13.2 Hz, 0.5H), 4.45 (br m, 1H), 4.27 (br d, *J*=11.6 Hz, 0.5H), 3.46-3.12 (m, 2H), 3.03 (br s, 1.5H), 2.89 (br s, 1.5H). MS (ESI) $(M+H)^+ = 420$. Anal. Calcd for $C_{23}H_{21}ClF_3NO$+1.2 TFA+0.1 H_2O: C, 54.62; H, 4.04; N, 2.51. Found: C, 54.63; H, 3.83; N, 2.52.

Example 26: 4-Chloro-α-[[[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol

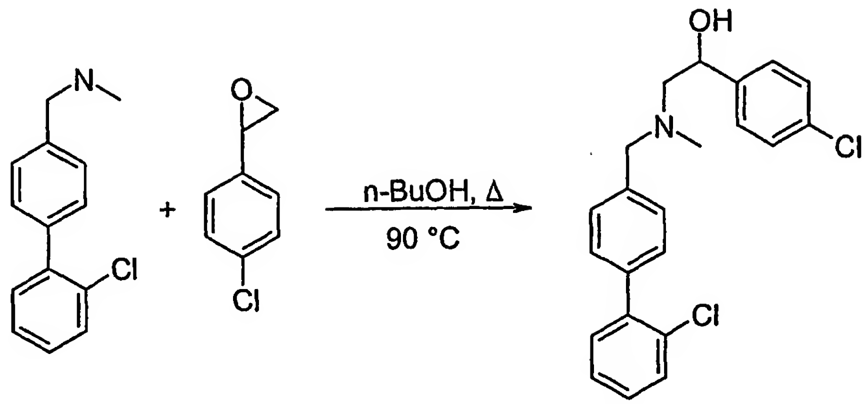


Compound 26a: 2'-Chloro-*N*-methyl-[1,1'-biphenyl]-4-methanamine



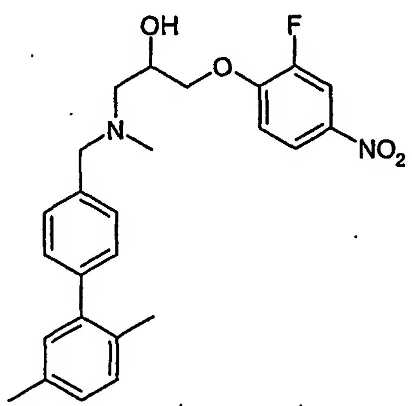
2'-Chloro-[1,1'-biphenyl]-4-carboxaldehyde (0.434 g, 2.00 mmol) was treated according to General Procedure 3 to provide the title compound (0.278 g, 75%). The crude material was of sufficient purity (>75%) to be used in subsequent steps. MS (ESI) $(M+H)^+ = 232$.

Compound 26b: 4-Chloro-α-[[[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol

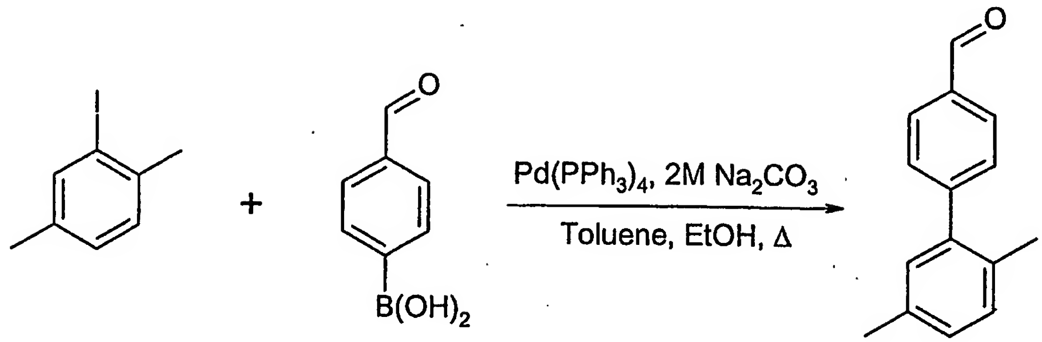


Following General Procedure 5, 2'-chloro-*N*-methyl-[1,1'-biphenyl]-4-methanamine (0.116 g, 0.50 mmol) and 2-(4-chlorophenyl)oxirane (0.078 g, 0.50 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH_3CN in H_2O) to provide the title compound (0.074 g, 30%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.63-7.50 (br m, 5H), 7.38 (br s, 7H), 5.11 (dd, *J*=3.4 Hz, *J*=10.6 Hz, 1H), 4.74 (br d, *J*=12.0 Hz, 0.5H), 4.47 (br s, 1H), 4.29 (br d, *J*=12.0 Hz, 0.5H), 3.41-3.17 (br d at 3.42, and br m, *J*=9.6 Hz for d, 2H), 3.05 (br s, 1.5H), 2.89 (br s, 1.5H). MS (ESI) $(M+H)^+$ = 386. Anal. Calcd for $C_{22}H_{21}Cl_2NO$ + 0.1 H_2O + 1.1 TFA: C, 56.60; H, 4.38; N, 2.73. Found: C, 56.49; H, 4.28; N, 2.70.

Example 27: 1-[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol

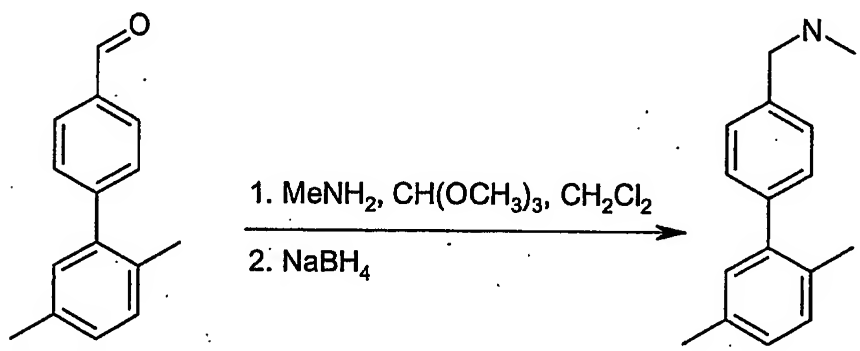


Compound 27a: 2',5'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde



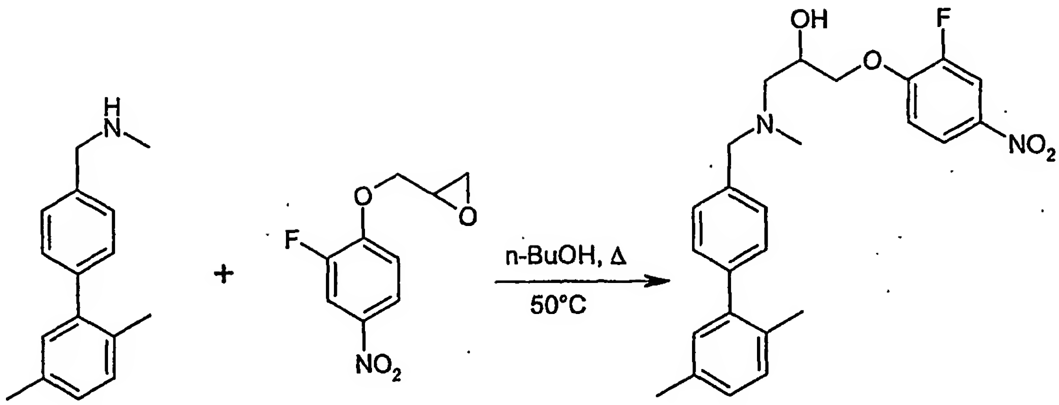
Following General Procedure 1, 2-iodo-1,4-dimethyl-benzene (2.06 g, 8.89 mmol), 4-formylphenylboronic acid (2.00 g, 13.34 mmol), $Pd(PPh_3)_4$ (0.51 g, 0.44 mmol), and 2 M Na_2CO_3 (31 mL, 62 mmol) were combined. Following the usual work-up provided the title compound (1.67 g, quantitative). The crude material was of sufficient purity (>90%) to be used in the subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 10.06 (s, 1H), 7.92 (dd, *J*=1.8 Hz, *J*=8.2 Hz, 2H), 7.49 (dd, *J*=1.6 Hz, *J*=8.4 Hz, 2H), 7.18 (d, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 7.05 (s, 1H), 2.36 (s, 3H), 2.23 (s, 3H).

Compound 27b: *N*,2',5'-Trimethyl-[1,1'-biphenyl]-4-methanamine



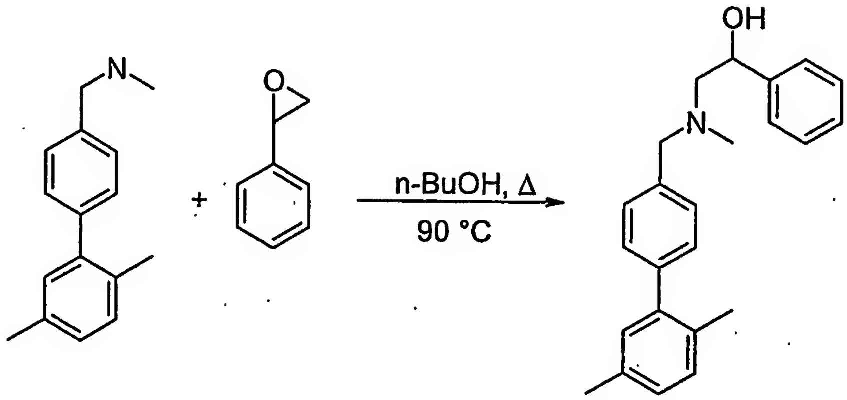
2',5'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde (0.263 g, 1.25 mmol) was treated according to General Procedure 3 to provide the title compound (0.203 g, 80%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. MS (ESI) $(M+H)^+$ = 226.

Compound 27c: 1-[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol



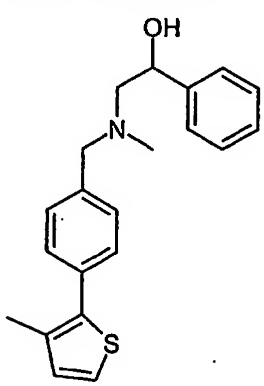
Following General Procedure 5, *N*,2',5'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.068 g, 0.30 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.64 g, 0.38 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH_3CN in H_2O) to provide the title compound (0.056 g, 34%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.08-8.00 (br m, 2H), 7.56 (d, *J*=8.4 Hz, 2H), 7.40 (d, *J*=8.4 Hz, 2H), 7.27 (br s, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 6.96 (s, 1H), 4.61, (br s, 0.5H), 4.46 (br s, 2H), 4.28-4.18 (overlapping br d at 4.26 and br s at 4.18, *J*=15.2 Hz, 2.5H), 3.54-3.22 (br d at 3.52, br s at 3.39, and br s at 3.22, *J*=12.4 Hz, 2H), 2.98-2.91 (overlapping br s at 2.98 and br s at 2.91, 3H), 2.29 (s, 3H), 2.15 (s, 3H). MS (ESI) $(M+H)^+$ = 439. Anal. Calcd for $C_{25}H_{27}FN_2O_4$ + 0.4 H_2O + 1.2 TFA: C, 56.49; H, 5.02; N, 4.81. Found: C, 56.46; H, 5.01; N, 4.86.

Example 28: α-[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol

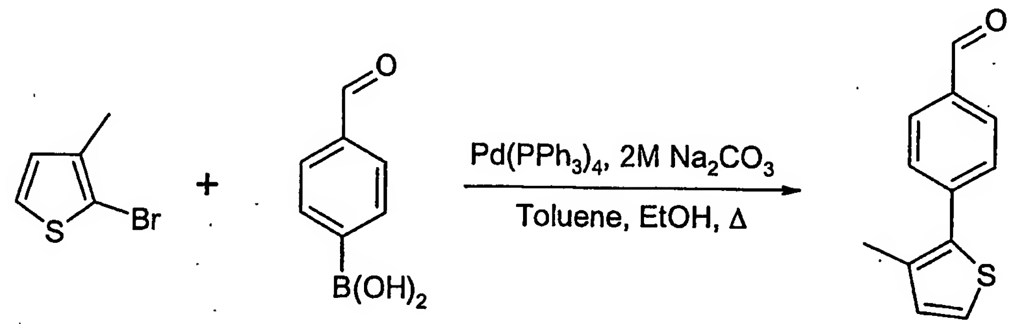


Following General Procedure 5, *N*,2',5'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.072 g, 0.32 mmol) and 2-phenyl-oxirane (0.038 g, 0.32 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH_3CN in H_2O) to provide the title compound (0.033 g, 22%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.54 (br s, 2H), 7.40-7.31 (br m, 7H), 7.13 (d, *J*=8.0 Hz, 1H), 7.05 (d, *J*=7.6 Hz, 1H), 6.98 (s, 1H), 5.08 (dd, *J*=3.6 Hz, *J*=10.8 Hz, 1H), 4.71 (br d, *J*=10.0 Hz, 0.5H), 4.44 (br s, 1H), 4.27 (br d, *J*=13.2 Hz, 0.5H), 3.41-3.16 (br d at 3.39, and br m, *J*=12.8 Hz for d, 2H), 3.03 (br s, 1.5H), 2.87 (br s, 1.5H), 2.29 (s, 3H), 2.16 (s, 3H). MS (ESI) $(M+H)^+ = 346$. Anal. Calcd for $C_{24}H_{27}NO + 0.6\ H_2O + 1.0$ TFA: C, 66.40; H, 6.26; N, 2.98. Found: C, 66.45; H, 6.16; N, 2.68.

Example 29: α-[[Methyl[[4-(3-methyl-2-thienyl)phenyl]methyl]amino]methyl]-benzenemethanol

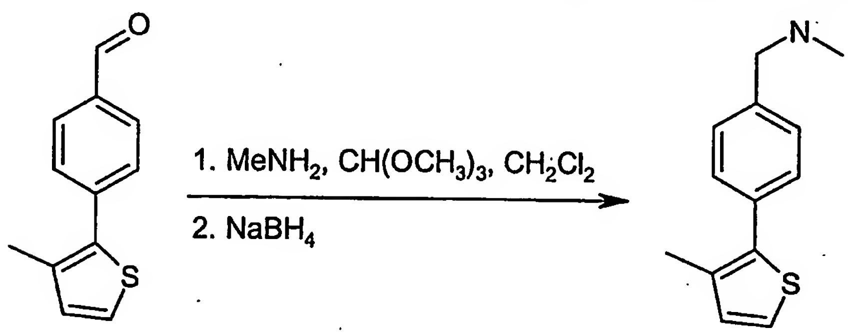


Compound 29a: 4-(3-Methyl-2-thienyl)-benzaldehyde



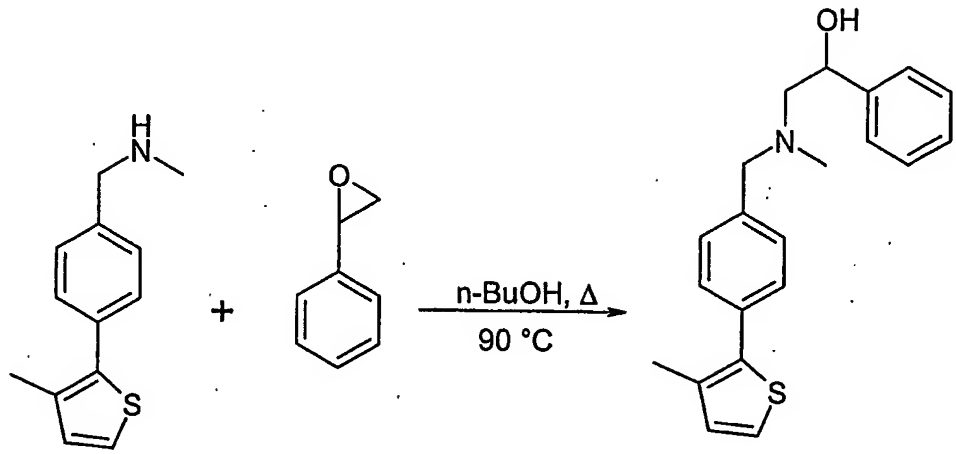
Following General Procedure 1, 2-bromo-3-methyl-thiophene (0.88 g, 4.95 mmol), 4-formylphenylboronic acid (1.11 g, 7.43 mmol), $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol), and 2 M Na_2CO_3 (15 mL, 35 mmol) were combined. Following the usual work-up provided the title compound (0.579 g, 58%). The crude material was of sufficient purity (>50%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 10.04 (s, 1H), 7.92 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=5.2 Hz, 1H), 6.97 (d, *J*=5.2 Hz, 1H), 2.39 (s, 3H).

Compound 29b: *N*-Methyl-4-(3-methyl-2-thienyl)-benzenemethanamine



4-(3-Methyl-2-thienyl)-benzaldehyde (0.253 g, 1.25 mmol) was treated according to General Procedure 3 to provide the title compound (0.139 g, 57%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.55 (d, *J*=8.4 Hz, 1H), 7.42 (d, *J*=8.4 Hz, 1H), 7.38-7.33 (overlapping d at 7.37, *J*=8.4 Hz, and d at 7.34, *J*=8.4 Hz, 2H), 7.18 (d, *J*=5.2 Hz, 1H), 6.91 (d, *J*=5.2 Hz, 1H), 3.77 (s, 2H), 2.47 (s, 3H), 2.32 (s, 3H). MS (ESI) $(M+H)^+$ = 218.

Compound 29c: α-[[Methyl[[4-(3-methyl-2-thienyl)phenyl]methyl]amino]methyl]-benzenemethanol



Following General Procedure 5, *N*-methyl-4-(3-methyl-2-thienyl)-benzenemethanamine (0.109 g, 0,50 mmol) and 2-phenyl-oxirane (0.060 g, 0.50 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-30% CH_3CN in H_2O) to provide the title compound (0.032 g, 14%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.62-7.57 (m, 4H), 7.42-7.33 (overlapping d at 7.33 and m, *J*=4.8 Hz for d, 6H), 6.96 (d, *J*=5.2 Hz, 1H), 5.12 (br s, 1H), 4.73 (br d, *J*=12.8 Hz, 0.5H), 4.45 (br s, 1H), 4.27 (br d, *J*=13.2 Hz, 0.5H), 3.43-3.18 (br d at 3.42, *J*=12.4 Hz, br d at 3.18, *J*=11.2 Hz, and br m, 2H), 3.04 (s, 1.5H), 2.88 (s, 1.5H), 2.33 (s, 3H). MS (ESI) $(M+H)^+ = 338$. Anal. Calcd for $C_{21}H_{23}NOS + 0.8\ H_2O + 1.1$ TFA: C, 58.38; H, 5.43; N, 2.93. Found: C, 58.48; H, 5.41; N, 2.93.

EXAMPLES 30- 132

Additional exemplary compounds were prepared according to the general procedures and the examples described above. Mass spectra of these compounds were obtained to confirm the formation of these compounds. These exemplary compounds and the mass spectrum results thereof are listed in Table 2 below.

Table 2

Example No.	Compound Name	MS (ESI) (M+H)+
30	1-[4-(1,1-Dimethylethyl)phenoxy]-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	472
31	1-[4-(1,1-Dimethylethyl)phenoxy]-3-[[(2'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-propanol	434
32	β-Ethoxy-*N*-methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]benzeneethanamine	414
33	*N*-Methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]glycylglycine, ethyl ester	409
34	*N*-Ethyl-2-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]acetamide	351
35	α-[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol	491
36	α-[[Methyl[(2,2',5'-trimethyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol	360
37	1-[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	513
38	4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile	466
39	1-[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	479
40	1-[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	451
41	4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-[1,1'-biphenyl]-2-carbonitrile	436
42	1-[[(2'-Chloro-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	459
43	1-[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	459
44	1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]-2-propanol	456

Example No.	Compound Name	MS (ESI) $(M+H)^+$
45	α-[[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]methyl]benzenemethanol	358/360
46	4'-[[(2-Hydroxy-2-phenylethyl)methylamino]methyl]- [1,1'-biphenyl]-2-carbonitrile	343
47	α-[[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	366/368
48	α-[[Methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	400
49	α-[[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	420/422
50	4'-[[(2-Hydroxy-2-phenylethyl)methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile	373
51	α-[[[(2'-Fluoro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	336
52	α-[[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol	386/388/390
53	Methyl 3-[4-[[(2-hydroxy-2-phenylethyl)methylamino]methyl]phenyl]-2-thiophenecarboxylate	382
54	α-[[Methyl[[2'-(1-methylethoxy)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	376
55	α-[[[(2'-Ethoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	362
56	α-[[Methyl[[2'-(2-propenyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	358
57	α-[[[(2'-Cyclopentyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	386
58	α-[[Methyl[[5'-methyl-2'-(1-methylethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	374
59	α-[[[(2'-Methoxy-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol	362
60	1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	493

Example No.	Compound Name	MS (ESI) $(M+H)^+$
61	α-[[[[5-(4-Bromophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol	386/388
62	α-[[[[5-(4-Chlorophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol	342
63	α-[[Methyl[[5-[3-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol	376
64	Methyl 3-[5-[[(2-hydroxy-2-phenylethyl)methylamino]methyl]-2-furanyl]-2-thiophenecarboxylate	372
65	α-[[Methyl[[4-(3-pyridinyl)phenyl]methyl]amino]methyl]benzenemethanol	319
66	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-[4-(1,1-dimethylethyl)phenoxy]-2-propanol	438
67	1-(4-Chlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	450
68	1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-phenoxy-2-propanol	416
69	1-[[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	423
70	α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzeneethanol	400
71	1-(1,1-Dimethylethoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	396
72	Methyl 2-hydroxy-2-methyl-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate	382
73	($β^1S$)-β-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-cyclohexanepropanol	372
74	1-(4-Chlorophenoxy)-3-[[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-propanol	422
75	1-[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol	388
76	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol	408

Example No.	Compound Name	MS (ESI) (M+H)+
77	1-Phenoxy-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	442
78	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(3,4-dichlorophenoxy)-2-propanol	476
79	1-[([1,1'-Biphenyl]-4-ylmethyl)-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	419
80	1-[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	433
81	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	453
82	1-(4-Nitrophenoxy)-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	487
83	($\alpha^1 S$)-α-[[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol	358
84	($\alpha^1 S$)-α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol	378
85	(2*R*)-3-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-hydroxypropyl butanoate	402
86	(2*R*)-2-Hydroxy-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propyl butanoate	436
87	Methyl 2-hydroxy-2-methyl-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate	408
88	1-(3-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	479
89	1-(4-Iodophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	542
90	1-(3-Fluorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	434
91	Ethyl 4-[2-hydroxy-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propoxy]-benzenecarboximidate	487
92	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(3-fluoro-4-nitrophenoxy)-2-propanol	445

Example No.	Compound Name	MS (ESI) (M+H)+
93	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	445
94	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	427
95	1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-phenoxy-2-propanol	376
96	1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	421
97	*N,N*-Diethyl-4-[3-[[(5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]-3-methoxybenzamide	509
98	Ethyl 4-[3-[[(5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate	451
99	4-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]-*N,N*-diethyl-3-methoxybenzamide	579
100	2-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]benzamide	493
101	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(3-methoxyphenoxy)-2-propanol	480
102	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(1*H*-indol-5-yloxy)-2-propanol	489
103	Ethyl 4-[3-[[[4'-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate	521
104	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-phenoxy-2-propanol	450
105	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	495
106	2-Fluoro-α-[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	404

Example No.	Compound Name	MS (ESI) (M+H)+
107	α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	370
108	α-[[[(2'-Chloro-6'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	366
109	α-[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	364
110	4-Chloro-α-[[[(2',5'-dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	380
111	α-[[Methyl[[4-(4-methyl-3-thienyl)phenyl]methyl]amino]methyl]benzenemethanol	338
112	1-(2-Fluoro-4-nitrophenoxy)-3-[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-propanol	497
113	1-[[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	479
114	1-(4-Fluorophenoxy)-3-[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-propanol	452
115	α-[[[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	404
116	2-Fluoro-α-[[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	422
117	4-Chloro-α-[[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	438
118	1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	513
119	1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	495
120	1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol	468
121	α-[[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	420

Example No.	Compound Name	MS (ESI) $(M+H)^+$
122	α-[[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]-2-fluorobenzenemethanol	438
123	4-Chloro-α-[[[[2-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	454
124	α-[[[(2-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	352
125	1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	475
126	1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	457
127	1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol	430
128	α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	382
129	α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	400
130	4-Chloro-α-[[[(2'-chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	416
131	α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-4-(trifluoromethyl)benzenemethanol	450
132	α-[[Methyl[[5-[2-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol	376